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The Components of Sampling Variance of ABO Gene Frequency Estimates

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INTRODUCTION

IN THE MARCH, 1956 ISSUE of this *Journal* there appeared two papers, one by Boyd who derived Bernstein's original variance formulas for ABO gene frequency estimates and also arrived at new formulas for Wiener's estimates, and another by DeGroot who, for the first time, gave explicit expressions for the variances of the maximum likelihood estimates. These developments are most timely and will undoubtedly facilitate the calculation of sampling variances of the blood group gene frequency estimates. Their formulas, however, have been reduced to the simplest form only from the purely algebraic viewpoint. The three sets of variance formulas: (1) of maximum likelihood estimates, (2) of Bernstein's unadjusted estimates, and (3) of Wiener's estimates, take three different appearances, indicate no obvious relation to each other, and thus do not lend themselves to any ready interpretation. In the following I shall propose some alternate forms, expressing each variance in terms of certain components, which will show the similarity and dissimilarity of the three sets of variance formulas. These forms will also facilitate the comparison of the relative efficiencies of the three methods of estimation. The arithmetic involved in using the new forms is not necessarily more laborious.

TWO ALLELES WITH DOMINANCE

The principle of analyzing a sampling variance into components may best be illustrated by first considering the simple case of two alleles with dominance. Let p and r be the frequencies of the alleles A and a in a randomly mating population ($p + r = 1$), and let n_D, n_R be the observed numbers of dominant and recessive individuals in a random sample of size $G = n_D + n_R$. The observed proportions of dominants and recessives in the sample will be denoted by $(D) = n_D/G$ and $(R) = n_R/G$, so that $(D) + (R) = 1$. Further, in accordance with the conventional notation in sampling theory, we use $\hat{r}$ to denote the sample estimate of the population r. For large samples the estimate (the bias of which is negligible) is

$$\hat{r} = \sqrt{(R)} \quad \text{or} \quad \hat{p} = 1 - \sqrt{(R)} \tag{1}$$

and its sampling variance, as is well known, is

$$V(\hat{r}) = V(\hat{p}) = \frac{1 - r^2}{4G}. \tag{2}$$

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Now note that the variance (2) may be written as

$$V(\hat{p}) = \frac{p(1-p)}{2G} + \frac{p^2}{4G} \tag{3}$$

or

$$V(\hat{r}) = \frac{r(1-r)}{2G} + \frac{(1-r)^2}{4G}. \tag{4}$$

In the simple case of two alleles, $V(\hat{p})$ in (3) is equal to $V(\hat{r})$ in (4), but this is not in general the case with multiple alleles. The expressions (3) and (4) are instructive. The first component is clearly the variance value that would have been obtained if there were no dominance, and thus, the exact number of *alleles A* and *a* were known in the sample of *2G* genes. Then the second component must represent the loss of information incurred by dominance and the consequent failure of complete identification of the *2G* genes. With multiple alleles, because an aggregate of any number of alleles may be regarded as one allele, our form (3) will apply for the gene which is dominant over all other alleles, and our form (4) will apply for the gene which is recessive to all other alleles. Having established this principle, we may proceed to examine the variances of ABO estimates.

MAXIMUM LIKELIHOOD ESTIMATES

The difficulty in estimating the ABO gene frequencies arises from the fact that two of the three alleles are "codominant" rather than one dominant over the other. As we shall see later, the inefficiency of Bernstein's estimation method is due to ignoring the information provided by the codominant phenotype and treating it as an ordinary dominant. The maximum likelihood method of estimation takes account of all of the four observed phenotypic proportions. Because of the lack of complete dominance of one allele over all other alleles, our variance formulas (3) and (4) are not applicable. However, we know that the maximum likelihood estimates must have a smaller variance than indicated by (3) or (4) since they take explicit account of the group AB individuals. Unfortunately, the maximum likelihood estimates of the gene frequencies ($\hat{p}$, $\hat{q}$, $\hat{r}$) cannot be individually expressed in terms of the four observed proportions in the sample.

Most of the following notations are conventional and need no explanation except that we shall use "hat" ($\hat{}$) to denote the maximum likelihood estimates. In all cases the variances of the estimates of p and of q take the same form with p and q interchanged. Hence, we shall give only the expressions for $V(\hat{p})$ and $V(\hat{r})$. The "information" formulas have been given by Stevens (1950). The variance formulas presented by DeGroot (1956, p. 40), when expressed in terms of components, may be written as

$$V(\hat{p}) = \frac{p(1-p)}{2G} + \frac{p^2}{8G}\left(1 + \frac{r}{pq+r}\right) \tag{5}$$

$$V(\hat{r}) = \frac{r(1-r)}{2G} + \frac{(1-r)^2}{8G} + \frac{r(p-q)^2}{8G(pq+r)} \tag{6}$$

Note that the fraction $r/(pq + r)$ is larger than .90 for most human populations and larger than .95 in many cases. For instance, in England where $p = .25$, $q = .05$,

TABLE 1

AB $2pq$	B $q^2 + 2qr$	"B-dominants"
A $p^2 + 2pr$	O r^2	A + O $(p + r)^2$
"A-dominants"	B + O $(q + r)^2$	Total = 1

$r = .70$, approximately, $r/(pq + r)$ is larger than .98. When either p or q is small, as in some American Indian populations, the variance (5) becomes practically the same as (3). Indeed, it will be identical with (3) if $q = 0$. The third component of (6) will be small when p and q do not differ widely, as among Chinese for whom $p = .24$ and $q = .21$ approximately. Again, if $q = 0$, (6) reduces to (4), as it should. These forms enable us to obtain quick approximations to the variances for certain populations.

BERNSTEIN'S UNADJUSTED ESTIMATES

Bernstein's original estimates are based upon the fact that the four phenotypes (blood groups) may be pooled into two "classes", one "dominant" and one "recessive", depending on which allele we are considering, and thus *formally* reducing the problem to the simple case of two alleles with dominance. As illustrated in table 1, if we regard the gene producing antigen B as the dominant allele, then AB and B would be "dominants" while A and O would be "recessives"; that is to say, the estimates will be based upon the two row-totals of the table. Similarly, if we regard the gene producing antigen A as the dominant allele, then AB and A would be counted as dominants and B and O counted as recessives, and the estimates will be based upon the two column-totals of the table. In estimating r, we regard AB, A, and B as dominants, and O as recessive. Thus, Bernstein's original estimates are

$$p' = 1 - \sqrt{(B + O)}, \qquad r' = \sqrt{(O)} \tag{7}$$

Since these estimates are formally identical with (1), it follows that their variances are

$$V(p') = \frac{p(1 - p)}{2G} + \frac{p^2}{4G} \tag{8}$$

$$V(r') = \frac{r(1 - r)}{2G} + \frac{(1 - r)^2}{4G} \tag{9}$$

Unlike (3) and (4), (8) here refers to the dominant gene with a frequency $p = 1 - (q + r)$, while (9) refers to the recessive gene with a frequency $r = 1 - (p + q)$. These two expressions have in general quite different values.

There is another interesting relationship between the variance of the maximum likelihood estimate and that of Bernstein's unadjusted estimate. The variance of the sum $p' + q' + r'$ is, as shown by Bernstein (1930) and Boyd (1956),

$$V(p' + q' + r') = \frac{pq}{2G(1 - p)(1 - q)} \tag{10}$$

On the other hand, noting that $(1 - p)(1 - q) = (p + r)(q + r) = pq + r$, our (5) may also be written as

$$V(\hat{p}) = \frac{p(1 - p)}{2G} + \frac{p^2}{4G}\left\{1 - \frac{pq}{2(p + r)(q + r)}\right\} \tag{5'}$$

Hence, the relation

$$V(\hat{p}) = \frac{p(1 - p)}{2G} + \frac{p^2}{4G}\{1 - G \cdot V(p' + q' + r')\} \tag{11}$$

WIENER'S ESTIMATES

While Bernstein used the "between column" and "between row" information of table 1, Wiener used the "within column" and "within row" information. For instance, concentrating solely on the second row of the table, Wiener arrived at the following estimate of p:

$$p^* = \sqrt{(A + O)} - \sqrt{(O)} \tag{12}$$

His estimate of r is the same as Bernstein's and will be omitted from discussion. The variance formula for $V(p^*)$, found by Boyd (1956. p. 30), may be put into the following form:

$$V(p^*) = \frac{p(1 - p)}{2G} + \frac{p^2}{4G} + \frac{pq}{2G(p + r)} \tag{13}$$

which is $V(p')$ given by (8) plus the term $pq/2G(p + r)$. This shows not only that $V(p^*)$ is larger than $V(p')$ but also tells us by how much it is larger. The ratio of these two variances may also be obtained with a minimum amount of algebra. Thus

$$\frac{\text{Wiener's } V(p^*)}{\text{Bernstein's } V(p')} = \frac{(13)}{(8)} = 1 + \frac{2q}{(2 - p)(p + r)} \tag{14}$$

as found by DeGroot. Various other ratios may be obtained in a similar way. It should be said that although Wiener's estimates are less efficient for the case of three alleles, they have the advantage that they can be easily extended to the case of four or more alleles whereas, to do so for the more efficient methods would be enormously more laborious.

SUMMARY

When there is dominance, the variance of a gene frequency estimate may be expressed in terms of a component due purely to sampling and a component due to dominance. In the case of the ABO system, where two of the three alleles are co-

dominant with each other, there exists a third component whose magnitude depends on how the estimate has been made.

If the four blood groups are arranged into a 2×2 table we may say that the maximum likelihood estimates utilize the full information provided by the four cells of the table; Bernstein's estimates utilize the between-row and between-column information; and Wiener's estimates utilize the information within one row and that within one column.

If we use the simple dominance scheme as the "standard" case, the sampling variance of the three methods of estimation may be put into the following forms for easy comparison:

Maximum Likelihood: $$V(\hat{p}) = \frac{p(1-p)}{2G} + \frac{p^2}{4G}\left\{1 - \frac{pq}{2(p+r)(q+r)}\right\} \qquad (5)$$

Bernstein: $$V(p') = \frac{p(1-p)}{2G} + \frac{p^2}{4G} \qquad (8)$$

Wiener: $$V(p^*) = \frac{p(1-p)}{2G} + \frac{p^2}{4G}\left\{1 + \frac{2q}{p(p+r)}\right\} \qquad (13)$$

The corresponding expressions for $V(\hat{q})$, etc., may be obtained by interchanging p and q. Similar expressions for $V(\hat{r})$, etc., have also been given.

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Data on the Occurrence of Hemoglobin C and Other Abnormal Hemoglobins in Some African Populations[1]

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HEMOGLOBIN C is an abnormal form of hemoglobin first recognized in two American Negro families (Itano and Neel, 1950; Kaplan, Zuelzer, and Neel, 1951). The occurrence of the hemoglobin appears to be conditioned by the presence of a single gene. In individuals heterozygous for the gene, some 30–40 per cent of the hemoglobin is of the abnormal type, and there results an asymptomatic 'carrier' condition, referred to as the hemoglobin C trait, and detectable with certainty only with biochemical techniques (Itano and Neel, 1950; Kaplan, Zuelzer, and Neel, 1951, 1953). In individuals homozygous for the gene, virtually all of the hemoglobin is abnormal, and there results a mild hemolytic anemia, hemoglobin C disease (e.g., Spaet, Alway, and Ward, 1953; Ranney, Larson, and McCormack, 1953; Levin, Schneider, Cudd, and Johnson, 1953; Terry, Motulsky, and Rath, 1954).

The present studies were undertaken with the primary objective of extending existing knowledge concerning the distribution of the gene responsible for hemoglobin C. However, the electrophoretic techniques employed in this survey also yielded information on the occurrence of other abnormal hemoglobins as well. In particular, data have been collected on the distribution of the gene responsible for the well known sickle cell hemoglobin (hemoglobin S), as well as on the genes associated with several other hemoglobin abnormalities to be mentioned later. The gene responsible for hemoglobin C appears to be either an allelomorph of, or closely linked with, the gene responsible for hemoglobin S (Ranney, 1954). For the present, we will consider these two genes as alleles, which, following the suggestion of Neel (in press), will be designated as hgb_1^C and hgb_1^S, respectively, the normal allele of these two genes being designated as hgb_1^A.

The presence of hemoglobin S is detected by the convenient and simple sickling test. In the past fifteen years, numerous studies have been published on the frequency of occurrence of positive sickling tests in various parts of the world (summaries in Neel, 1951; Hiernaux, 1952; Singer, 1953; Mourant, 1954). By contrast, both because of the recency of its discovery and the greater difficulties in its detection, much

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less is known concerning the distribution of the hgb_1^C gene. With one exception (Diggs, Kraus, Morrison, and Rudnicki, 1954), hemoglobin C has thus far been encountered only in persons known to be in whole or part of Negro descent. About 2.2 per cent of American Negroes are heterozygous for the hgb_1^C gene, either in combination with its normal allele or with the hgb_1^S gene (Smith and Conley, 1953; Schneider, 1954; Dobson and Hettig, 1956). The relatively few studies thus far published concerning African Negroes have suggested a rather remarkable restriction in the distribution of the gene in Africa. Edington and Lehmann (1954), in a sample of 200 Gold Coast natives, detected 21 (10.5 per cent) who by paper electrophoresis appeared to be heterozygous for hgb_1^C (i.e., hgb_1^C/hgb_1^A), two apparently heterozygous for both hgb_1^C and hgb_1^S (hgb_1^C/hgb_1^S), and one apparently homozygous for hgb_1^C. An additional 34 persons (17 per cent) exhibited the sickle cell trait (hgb_1^S/hgb_1^A) while two persons, on the basis of paper electrophoresis, were thought to be homozygous for hgb_1^S. On the other hand, Jacob (1955) reported finding no persons with the hemoglobin C trait in 500 blood specimens obtained in Uganda. Roberts and Lehmann (1955) likewise found no hemoglobin C in 75 blood specimens obtained from southern Sudanese, all of whom lacked the sickle cell trait, and also no hemoglobin C in 100 natives of Tanganyika, of whom 12 had the sickle cell trait. Lehmann and Mackey (1955) found no hemoglobin C in 104 blood specimens obtained from East Africans living in Dar-es-Salaam.

Brain (1955) found two instances of the hemoglobin C trait among 219 Cape Town 'coloreds,' in whom the incidence of sickling is known to be about 0.6 per cent. The significance of this observation is difficult to evaluate because of the importation into this area of a small number of slaves from West Africa. At the moment, the southern limits in Africa of the distribution of the hgb_1^C gene are, with the exception of Brain's two cases, set by the description of a case of sickle cell-hemoglobin C disease in a native of Portuguese Cabinda, on the west coast (Vandepitte and Colaert, in press). The northern limits of the distribution are set by the description of the occurrence of hemoglobin C in an Algerian family (Portier, Cabannes, Massonnat, and Duval, 1954). There is thus evidence for a relatively much higher frequency of the hgb_1^C gene in West than in East Africa. This is in marked contrast to the much wider distribution of the hgb_1^S gene, which is not only found with varying frequency throughout most of Africa south of the Sahara, but in Greece and India as well.

In the course of the present studies, blood specimens have been collected in three widely separated areas in Africa, as follows: (1) in the eastern Congo and Ruanda-Urundi, by Hiernaux, utilizing as a source either plantation laborers (Shi), rural populations (Imbo), or students and rural populations (Tutsi), (2) in Liberia, by Livingstone and Neel, utilizing primarily laborers on the Firestone Plantation, and (3) in Dakar, by Linhard, utilizing prospective blood donors at the Centre Fédéral de Transfusion Sanguine. Strictly speaking, none of these is a random sample of the population, both because the individuals serving as subjects were selected as to health (ability to perform work or acceptability as a blood donor) and age (adults only). The specimens were obtained in 10 cc. venules which, after refrigeration, were shipped by air in thermos flasks to the Child Research Center, Detroit, Michigan, where the hemoglobin content of each specimen was determined and the sample

TABLE 1. THE OCCURRENCE OF ABNORMAL HEMOGLOBINS IN CERTAIN AFRICAN TRIBES OF RUANDA URUNDI AND ADJACENT CONGO AREAS. THE LETTERS HEADING THE COLUMNS REFER TO THE HEMOGLOBIN PATTERNS ON PAPER ELECTROPHORESIS.

Tribe	Composition of hemoglobin					Total
	A	AS	AC	S	C	
Imbo	266	62	—	—	—	328
Shi	289	12	—	—	—	301
Tutsi	304	2	—	—	—	306
Total	859	76				935

TABLE 2. THE OCCURRENCE OF ABNORMAL HEMOGLOBINS IN CERTAIN AFRICAN TRIBES OF FRENCH WEST AFRICA

Tribe	A	AS	AC	S	C	Total
Bambara	36	9	3	—	—	48
Diola	6	—	—	—	—	6
Foula	17	4	—	—	—	21
Laobé	14	—	—	—	—	14
Lebou	27	2	—	—	—	29
Mandengo	33	—	—	—	—	33
Mauré	8	1	1	—	—	10
Oulof	252	27	2	—	1*	282
Peul	38	4	—	—	—	42
Saracolé	10	4	—	—	—	14
Sérère	291	12	—	—	—	303
Soussou	11	6	1	—	—	18
Toucouleur	56	19	3	1*	—	79
Miscellaneous	47	9	5	—	—	61
Total	846	97	15	1	1	960

* Discussion of this individual in text.

then analyzed for the presence of an abnormal hemoglobin by the method of paper electrophoresis, with apparatus and under conditions which have been described elsewhere (Zuelzer, Neel, and Robinson, 1956). Additional studies on hemoglobin solubility in a phosphate buffer (cf. Itano, 1953) and rate of denaturation in an alkali solution (cf. Singer, Chernoff, and Singer, 1951a, b) were carried out as indicated.

THE FINDINGS

The findings of the study are summarized in Tables 1, 2, and 3. The hemoglobin or combination of hemoglobins present in any specimen is indicated by the appropriate letters. Thus, the designation AC indicates that hemoglobins type A and type C were detected on paper electrophoresis. In the eastern Congo and Ruanda-Urundi, no hemoglobin C was detected among 935 specimens tested, in keeping with the observations of Jacob (1955) and of Roberts and Lehmann (1955) in neighboring regions. No hemoglobin C was observed in a tribe with a considerable frequency of the sickle cell trait (the Imbo, 18.8 per cent sickle cell trait), in a tribe with a low frequency of the sickle cell trait (the Shi, with 4 per cent), and in a tribe with a strong Hamitic element (the Tutsi, 1.9 per cent sickle cell trait). The morphological and serological characteristics of these tribes have recently been described in detail by Hiernaux (1953, 1954).

TABLE 3. THE OCCURRENCE OF ABNORMAL HEMOGLOBINS IN CERTAIN AFRICAN TRIBES OF LIBERIA. THE HEMOGLOBIN LABELED "FAST" IS DISCUSSED IN THE TEXT

Tribe	A	AS	AC	S	C	"Fast"	Total
Bassa	161	16	—	1*	—	1	179
Buzzie	90	12	1	—	—	2	105
Gbande	39	3	—	—	1*	—	43
Gio	43	1	—	—	—	1	45
Gissi	55	10	—	—	—	—	65
Gola	29	3	—	—	—	1	33
Grebo	6	1	—	—	—	—	7
Kpelle	156	18	3	1*	—	3	181
Krahn	40	—	—	—	—	—	40
Kru	39	1	—	—	—	—	40
Mano	88	4	1	—	—	1	94
Mende	19	5	—	—	—	—	24
Vai	17	2	—	—	—	—	19
Miscellaneous	21	7	1	—	—	—	29
Total	803	83	6	2	1	9	904

* These individuals will be discussed in detail in the text.

Among 960 specimens from Dakar, 15 (1.6 per cent) exhibited the hemoglobin C trait; one additional specimen appeared by paper electrophoresis to be homozygous for the hemoglobin C gene. This latter was an unexpected finding in view of the frequency of heterozygotes. Practically all of the principal tribes of the western portion of French West Africa were represented among the donors of the specimens collected in Dakar. However, the data on any one tribe are not sufficiently extensive to permit conclusions concerning tribal differences in the frequency of hemoglobin C. In this same group, the over-all frequency of the sickle cell trait was 10.1 per cent; one blood specimen was encountered which on paper electrophoresis appeared to consist only of hemoglobin S.

In Liberia, only 6 in a total of 905 individuals (0.7 per cent) were found to have the hemoglobin C trait. One additional individual was observed who by electrophoresis appeared to be homozygous for the C gene, again a somewhat unexpected finding in view of the rarity of the heterozygotes. The possible significance of this individual, as well as the one observed in Dakar, will be discussed later. Hemoglobin C would thus appear to be less common in Liberia than Dakar, despite the greater proximity of Liberia to the Gold Coast. Because laborers for the Firestone Plantation are recruited from all over Liberia, representatives of most of the principal tribes of this country are included among the 905 donors of specimens. There is no obvious tendency for hemoglobin C to occur in any particular tribe, although with these numbers small differences between tribes in this respect could easily be missed. The over-all frequency of the sickle cell trait in this group is 9.2 per cent. This figure, which is confirmed by extensive unpublished figures of Livingstone, is significantly less than has been observed in other nearby West African groups. This low frequency is not to be attributed to the genetic influence of the repatriated slaves who founded Liberia, since their descendants have intermarried with the local tribes only to a limited extent; the Americo-Liberians encountered in this study have been included with the 'miscellaneous' group of Table 3. Two individuals were encountered who on

paper electrophoresis appeared to possess only hemoglobin S. The interpretation of this finding will be discussed in the next paragraph. The Liberians studied were also unusual in the occurrence, in 9 individuals (1.0 per cent), of a hemoglobin component which on paper electrophoresis at pH 8.6 migrated more rapidly than normal hemoglobin (hemoglobins S and C migrate more slowly than normal). Two different hemoglobin components seem to be involved, neither corresponding precisely to any previously described. This finding will be discussed in detail elsewhere (Zuelzer, Robinson, Livingstone, Neel, and Miller, in manuscript).

As has been noted, we have encountered in the course of this study three blood specimens which appeared by paper electrophoresis to consist almost entirely of hemoglobin S, one from Dakar and two from Liberia. In view of the frequency of the hgb_1^S gene in these two areas, and the usual sublethal effects in Africa of the gene when homozygous (Vandepitte, 1954; the Lambotte-Legrands, 1955), one would not expect to encounter in a sample of this size this number of homozygous individuals. The Dakar specimen was from a male Toucouleur, estimated age 28, whose hemoglobin level was 11.5 gms.%, who had 13.2% alkaline resistant hemoglobin by the Singer method, and whose hemoglobin solubility in a 2.24 M phosphate buffer was 0.88 gms. per liter. The specimens from Liberia were obtained from an adult Bassa male and an adult Kpelle male, whose hemoglobin levels were 11.5 and 11.6 gms.% respectively, who had 6.6 and 1.9% alkaline resistant hemoglobin by the Singer method respectively, and whose hemoglobin solubility in a 2.24 M phosphate buffer was 0.64 gms. and undetermined, respectively. Although the biochemical findings in these three individuals are those characteristic of homozygosity for the hgb_1^S gene, the hemoglobin level is well above that usually seen in individuals of this genotype.

Edington and Lehmann (1955a) have recently described two similar individuals from the Gold Coast, and Jacob (1956) has encountered several similar cases in Uganda. In the absence of any evidence for the occurrence of the thalassemia gene in West Africa, Edington and Lehmann (1955a) were inclined to interpret their cases as being of the genotype hgb_1^S/hgb_1^S, which genotype had for some reason not resulted in the usual severe hemolytic anemia. Because these cases were so counter to clinical experience in the United States with the results of homozygosity for the hgb_1^S gene, one of us was led to suggest shortly after this report appeared that these cases might actually be due to simultaneous heterozygosity for the hgb_1^S gene and some other, as yet unidentified gene (cf. Neel, in press). Genetic evidence that this is the likely explanation has now been forthcoming, in the observation that both of these individuals have children whose erythrocytes fail to sickle (Edington and Lehmann, 1955b). However, these non-sickling children, although non-anemic and with normal-appearing blood films, did have increased amounts of fetal hemoglobin. This suggests the existence in West African populations of a previously undescribed genetic factor which thus far can be recognized solely through the increase it occasions in the amount of fetal hemoglobin, or in its interaction effects.

Although it has not yet been possible to examine the parents or children of the three 'high-S' individuals encountered in the present study, it seems quite likely

that at least the two individuals with the increased amounts of fetal hemoglobin are further examples of the entity described by Edington and Lehmann (1955a). Support for this viewpoint comes from the following fact: during the course of the studies of the hemoglobin specimens from Liberia, a number of electrophoretic determinations yielding a single spot in the position of hemoglobin A were thought to show suspicious 'tailing'. Alkaline denaturation studies run on such hemoglobins revealed in a number of instances, fetal (alkaline resistant) hemoglobin in amounts exceeding the upper limits of normal in Caucasian populations (2 per cent). Detailed studies of the frequency of occurrence of individuals with increased amounts of fetal hemoglobin are in progress. Even at this stage, however, these findings lend confirmation to the suggestion that the three 'high-S' individuals here described have the same genetic explanation as those encountered by Edington and Lehmann. Edington and Lehmann (1955b) refer to this as a "thalassemia-like" gene. The appropriateness of this term is debatable. The gene in question does not seem to have the cytological effects associated with the already known thalassemia gene(s). Furthermore, although this factor is similar to the thalassemia gene in elevating the alkaline resistant (fetal) component of adult hemoglobin, on the face of the existing evidence it would appear to be more effective in this regard than the thalassemia gene(s), although there is of course no way at present of estimating what proportion of heterozygotes for this gene fail to show an elevation of the alkali resistant fraction. Incidentally, the fact that individuals simultaneously heterozygous for this gene and the hgb_1^S genes are clinically normal, although from the standpoint of their hemoglobin apparently biochemically identical with hgb_1^S/hgb_1^S individuals, raises the possibility that the characteristic clinical picture of the hgb_1^S/hgb_1^S individual is due to something more than the hemoglobin abnormality.

We have already mentioned the occurrence of two blood specimens, one from Dakar and one from Liberia, which on paper electrophoresis appeared to be composed entirely of hemoglobin C. These were unexpected observations, inasmuch as in Liberia, with a frequency of the hgb_1^C gene of approximately 0.003, homozygotes should have a frequency of 0.000009, while in Dakar, with a gene frequency of 0.008, the corresponding homozygote frequency would be 0.000064. The Liberian native whose hemoglobin appeared to be composed exclusively of hemoglobin C was an adult male Gbande whose hemoglobin level was 12.8 gms.%. The amount of alkali-resistant (fetal) hemoglobin present was 3.6 per cent of the total. Solubility of the hemoglobin in a 2.58 M phosphate buffer was 3.8 gms. per liter. The specimen from the Dakar native was unfortunately discarded before alkali resistance and solubility studies were carried out. The relatively high solubility of the hemoglobin in the first specimen is in keeping with previous reports concerning individuals whose hemoglobin was predominantly of the C type (Itano, 1953), and provides confirmation of the correctness of the electrophoretic findings. By analogy with the genetic situation described above as regards hemoglobin S, the possibility must be entertained that the two individuals whose electrophoretic picture is that of homozygosity for the hgb_1^C gene actually possess only a single hgb_1^C gene, whose expression has been modified by another genetic factor present in the population. Critical evidence

regarding this suggestion will be derived from detailed family studies on these or comparable individuals. We have thus far been unable to reestablish contact with these persons.

The problem of identifying the occurrence of hemoglobin D in a survey study such as this should be mentioned. This hemoglobin has the same electrophoretic mobility as hemoglobin S on paper electrophoresis, but is distinguished by its failure to be associated with the sickling phenomenon, and its greater solubility (Itano, 1951). Sickling tests were performed in Africa on most of the blood specimens on which this report is based; a few instances were encountered where there was a discrepancy between the results of the sickling test and the results of paper electrophoresis. Unfortunately, it was not feasible to check back to these specimens, to rule out the possibility of a technical error in the sickling test. Theoretically, it should be possible to make the distinction on the basis of solubility studies, and in fact among a total of 256 specimens which on paper electrophoresis appeared to be AS and on which solubility studies were done, we have encountered two instances where the solubility of the hemoglobin was in the normal range. These could actually be AD rather than AS bloods.

DISCUSSION

These data, taken in conjunction with those already in the literature, present certain aspects of unusual anthropological interest. Figure 1 depicts graphically the distribution of the hgb_1^C gene in Africa as it is now known. In drawing Figure 1, we have indicated the average frequency of the hemoglobin C trait in political subdivisions. However, at the time of the partition of Africa by the Great Powers, these political subdivisions were formed with no particular reference to tribal distributions or affinities, so that not only may a given subdivision be quite heterogeneous, but it may also cut across tribal lines. The most meaningful maps would be on a tribal basis. Unfortunately, the data are not yet sufficiently detailed for the preparation of such maps. Some misimpressions which are perhaps conveyed by the present map will be discussed shortly.

In the preparation of Figure 1, in addition to the sources already referred to, four unpublished studies have been taken into consideration. We are greatly indebted to the authors of these studies for permission to quote their results in advance of publication. Vandepitte (personal communication) found no hemoglobin C in 400 blood specimens obtained in the central Congo, in a region where about 25 per cent of the natives have the sickle cell trait. Allison (personal communication) in an extensive survey of African populations, has encountered the following frequencies of persons heterozygous for hgb_1^C: Gambia—1.8 per cent; Sierra Leone—4.6 per cent; the Gold Coast—11.0 per cent; Nigeria—5.3 per cent; and Tanganyika—0.0 per cent. Edington and Lehmann (personal communication), in an extension of their earlier studies, observed among 183 natives of the southern Gold Coast 34 with the AS pattern, 16 (8.7 per cent) with the AC pattern, 1 with SC, and 1 with AG, the remainder being normal; and among 283 from the Northern Territories of the Gold Coast, 17 with AS, 57 (20.1 per cent) with AC, 2 with SC, and 2 with C, the remainder being normal. Finally, Lehmann and Walters (personal communication) observed that 18 per cent

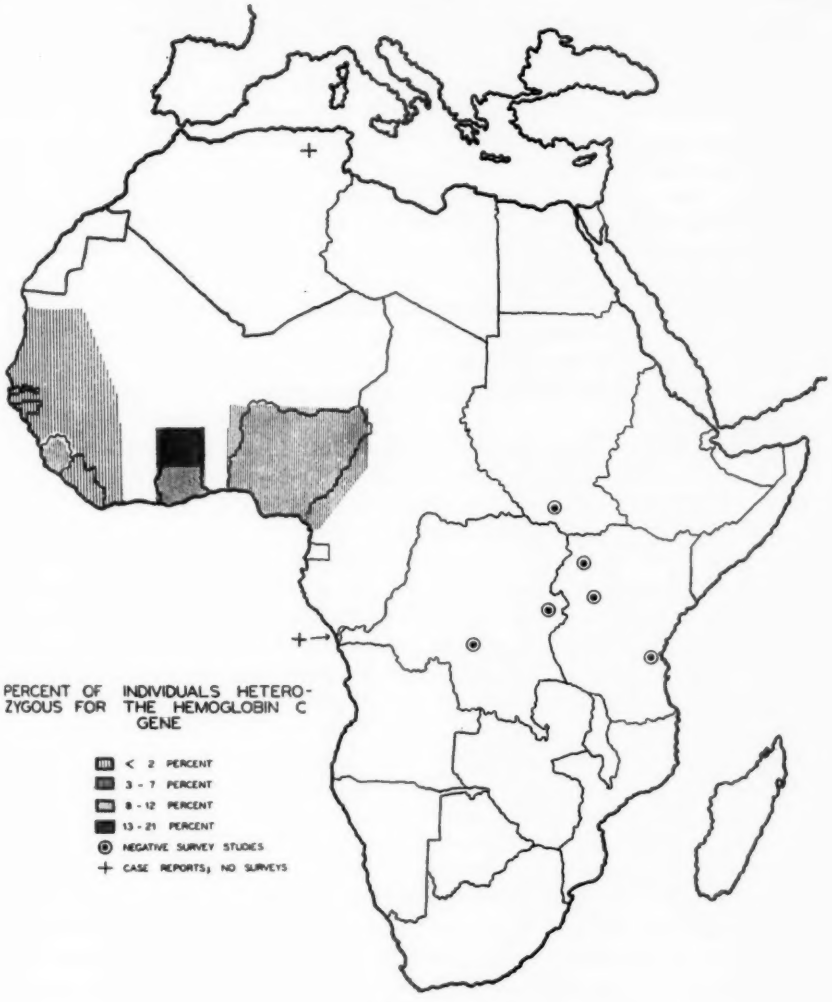

FIGURE 1

of 155 Igala from Nigeria were AS, but none possessed hemoglobin C, whereas of 940 Yuroba, 236 were AS and 67 were AC.

As pointed out by Neel (in press), on the basis of much more fragmentary information, the data on the distribution of the hgb_1^C gene "suggest a highly localized, 'diffusion gradient' type of gene distribution, centering around the Gold Coast. This could be interpreted as the finding to be expected for a gene of relatively recent origin with a high selective value." If future work corroborates this suggestion, then here is a most unusual opportunity to investigate the processes through which, fol-

lowing its origins, a gene with a selective advantage becomes disseminated throughout an area. Whether this postulated selective advantage involves only heterozygotes, leading to a 'balanced polymorphism,' or both heterozygotes and homozygotes, with the prospect of ultimate replacement (under existing conditions) of the normal allelomorph, is unknown. However, the study of this genetic system is complicated by the occurrence of the hgb_1^S allelomorph. There is already abundant evidence that this latter gene is involved in a complex selective system, maintaining its relatively high frequencies because of 'balanced polymorphism,' with, on the basis of present information, the most important single factor in achieving this balance possibly a diminished susceptibility of the hgb_1^S/hgb_1^A individual to *P. falciparum* malaria (review in Allison, 1954; Neel, in press). Because of the possible relationship between hemoglobin type and the ability of the malaria parasite to establish itself, a differential susceptibility to malaria on the part of individuals with and without hemoglobin C is certainly also the first explanation of the frequency of the hgb_1^C gene to be investigated.

In non-malarious regions (i.e., the United States), the genotypes now known to compose this system can be tentatively ranked in the following order with regard to 'fitness' (i.e., ability to survive and reproduce): $hgb_1^A/hgb_1^A = hgb_1^C/hgb_1^A = hgb_1^S/hgb_1^A > hgb_1^C/hgb_1^C > hgb_1^C/hgb_1^S > hgb_1^S/hgb_1^S$. Although we have indicated no differences between the first three genotypes, the relative inability of hgb_1^S/hgb_1^A individuals to concentrate their urine (Zarafonetis et al., 1955; Scott et al., 1955; Keitel and Thompson, 1956) suggests that under arid conditions this genotype would be found less fit than the other two. The available data are insufficient to permit a similar ranking of the genotypes for African conditions, let alone specifying a selective advantage for each genotype. Thus, it is not known whether hgb_1^C/hgb_1^A or hgb_1^S/hgb_1^A is the fitter genotype under West African conditions, nor whether, under these same conditions, the hgb_1^C/hgb_1^C individual is more or less fit than hgb_1^A/hgb_1^A. If, however, one assumes that the fitness of the above-listed six genotypes is approximately constant throughout the highly malarious coastal and subjacent regions extending from Gambia to the Belgian Congo, it follows that the genetic system involved is in a state of marked instability. Inasmuch as in general, if the selective factor is constant, the populations with the higher total (combined) frequencies of hgb_1^C and hgb_1^S are more apt to represent equilibrium values than those with lower frequencies, the population of the Gold Coast would appear to be most nearly in equilibrium of all those studied, and the population of Liberia the farthest removed from equilibrium. Otherwise stated, if the present gene frequencies in this area represent equilibrium values, there are unknown selective differentials from place to place—malaria can scarcely be the major agent of selection in this system, in view of its hyperendemicity throughout this region.

The detailed studies which are necessary for an understanding of the manner of diffusion of the hgb_1^C gene throughout West Africa have scarcely begun. Of particular interest will be the ultimate explanation of 'breaks' in the cline. In Figure 1 we have indicated Sierra Leone as an 'island' of higher hgb_1^C frequency than the surrounding regions. However, on the basis of the present data, it would be almost equally appropriate to regard Liberia as an 'island' of lower hgb_1^C frequency. Thus, of all the

tribes whose representatives in Dakar were studied with respect to the occurrence of hemoglobin C, the Bambara have a tribal distribution most nearly north of Liberia. Three of the 48 (6.3 per cent) Bambara sampled appeared to be heterozygous for the hgb_1^C gene. While the numbers are far too small to permit generalization, the possibility is raised that the frequency of the hgb_1^C gene to the north of Liberia is more like the frequency in Sierra Leone than that in Liberia, in which case Liberia might well turn out to be the 'island.'

Further evidence suggesting that at least some of the tribes included within the boundaries of Liberia may have biological traits in common which differentiate them from their neighbors, comes from a consideration of the known facts regarding the distribution of the hgb_1^S gene in this region. Table 3 reveals that the over-all frequency of the sickle cell trait in Liberia is in the neighborhood of 9 per cent. On the basis of extensive unpublished studies by one of us (F.B.L.), and as already suggested by Table 3, it appears that there are marked differences among the tribes found in Liberia with respect to the frequency of the sickle cell trait. This may best be described as a northwest-southeast cline, the Vais, Golas, Mendes, Gbandes, and Gissi to the northwest having trait frequencies of approximately 15 per cent, the Gio, Krahn, Kru, and Gissi to the southeast having trait frequencies of 1–4 per cent. To the northwest of Liberia, in immediately adjacent Sierra Leone, the frequency of the sickle cell trait is approximately 25–30 per cent (Gosden and Reid, 1948; Rose and Suliman, 1955). There are no figures for the Ivory Coast, Liberia's neighbor on the other side, but in the Gold Coast, just east of the Ivory Coast, the over-all frequency of the sickle cell trait, as already noted, approximates 17 per cent. Data for the region to the north of Liberia are extremely scanty. From the tribal distribution maps prepared by Pales in 1949, and published by the Service Géographique of French West Africa, the principal tribes to the north of Liberia, in French West Africa, are, proceeding from west to east, the Foula, Malinké, Bambara, Sénoufo, and Bobo. Pales and Linhard (1951) observed the following sickling frequencies in four of these five tribes: Malinké—21 per cent of 38 tests; Bambara—8.3 per cent of 108 tests; Sénoufo—27 per cent of 11 tests; and Bobo—7.7 per cent of 13 tests. Linhard (1952) records 10.3 per cent sickling among 146 Foula, and 8.4 per cent among 214 Bambara. Other data concerning the frequency of sickling in the last named of these tribes, collected in the course of nutritional surveys, has kindly been made available to us by Dr. Raoult of the Organisme de Recherches pour l'Alimentation et la Nutrition Africaines, Dakar. In the course of two village surveys, 33.8 per cent of 121 Bobo children were found to sickle in one village, and 15.6 per cent of 96 children of another village. Finally, our own fragmentary data on the Foulas (19 per cent of 21 tests) and Bambara (18.7 per cent of 48 tests) are in satisfactory agreement with the above. The combined figures are: Foula—19 (11.4 per cent) of 167; Malinké—8 (21 per cent) of 38; Bambara—36 (9.7 per cent) of 370; Sénoufo—3 (27 per cent) of 11; and Bobo—57 (24.8 per cent) of 230. By and large, then, these tribes exhibit sickle cell trait frequencies in reasonable agreement with those encountered in the tribes in the northwest half of Liberia, but in striking contrast to those in the southeast. The latter tribes are clearly set apart from those thus far studied in this general region of West Africa by these very low sickle cell trait fre-

quencies. Further evidence in support of regarding the tribes of Liberia as having some distinctive biological characteristics comes from the occurrence in approximately 1 per cent of Liberians of one or more otherwise very rare gene(s) responsible for a fast-moving hemoglobin component. Serological studies designed to shed additional light on the biological composition of these Liberian tribes are in progress.

A detailed study of the distribution of hemoglobin C in West Africa should yield information concerning the predominant streams of migration in this area. For instance, a preponderance of east-to-west migration should result in a more rapid fall off in gene frequency to the east of the peak frequency than to the west, unless the origin of the gene is very recent (post-migrational). There is thus the need for correlating the distribution of the gene with the available anthropological data; a conflict between the two would give cause for pause. There are too many gaps in the present data to permit any conclusions, but it must be admitted that there is little in the present findings to suggest the 'tear-drop' distortion of the gene distribution to be expected of migration. Otherwise stated, if further studies establish a selective value for hemoglobin C, a point not now known, then a detailed study of the distribution of this gene might shed light on migration in West Africa in recent times.

Finally, a few words should be written concerning the implications of the known distribution of the hemoglobin C gene for the problem of the origins of the American Negro. The latter, with 2.2 per cent heterozygotes for the hemoglobin C gene, has on the basis of both sociological and gene frequency data been estimated to be approximately one-fifth to one-third non-African in his genetic constitution (Herskovits, 1942; Neel, 1951; Roberts, 1955; Glass, 1955). This would imply that the frequency of heterozygotes for the C gene in the African ancestors of the American Negro averaged about 2.8 per cent. Such an average frequency could of course be achieved on the basis of a multitude of systems of sampling the African population. However, on the basis of the existing data, the over-all impression is that the regions west of the Gold Coast and south of Nigeria contributed to the origins of the American Negro at least as heavily as the region between the western border of the Gold Coast and the eastern border of Nigeria, despite the time-honored designation of the coast of much of this latter area as the "Slave Coast."

SUMMARY

Data are presented concerning the distribution of hemoglobin types in Africa, as determined by paper electrophoresis of blood specimens obtained in Ruanda-Urundi and the eastern Belgian Congo, in Liberia, and in the Dakar region of French West Africa. On the basis of these data, plus the other similar studies to date, a map has been constructed of the distribution in Africa of individuals heterozygous for the gene responsible for the formation of hemoglobin C. The implications of the distribution exhibited by this gene are discussed.

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The Frequency of First Cousin Marriages in a South Swedish Rural Community

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ALL MARRIAGES, contracted in the South Swedish community of G-B during the years 1901–1952, have been examined genealogically in order to determine the rate of first cousin marriages. This community was selected at random among 212 rural communities in the southernmost and most densely populated county of Sweden (Malmöhus län). The community happened to be situated in a district that was, in 1930, intermediate with regard to the percentage of residents born within the community, and in this respect representative of about ¼ of the area of a larger region studied by Bergsten (1951), comprising 78 per cent of the Swedish population (Svealand, excepting Dalarna, and Götaland).

The community was, within an area of 55 sq. km. of dry land, inhabited by 2,228 people in 1901 and 1,187 in 1952 (Table 1). Gains or losses through migration are presented in Table 1. G-B is an agricultural community without industry except a tilery, built in 1884 and employing, in 1952, 42 workmen. G-B has a highway, several byways and, since 1874 and 1884, respectively, two railways.

Data for the investigation were secured through marriage records, parish registers, and birth records. Of 576 marriages between 569 men and 574 women 10, or 1.7 per cent, were between first cousins. In the period 1901–1913 the rate of first cousin marriages was 4/162, 1914–1926 it was 3/163, 1927–1939 the rate was 3/148, and in 1940–1952 none of the 103 marriages embodied first cousins.

These figures make for the minimum incidence of first cousin marriages in G-B. The 10 first cousin marriages occurred among 457 couples with ancestries ascertainable in sufficient detail to determine if the partners were in fact first cousins. The maximum incidence of observed first cousin marriages in the community under study was, then, 2.2 per cent. If 119 marriages are considered half-examined, the frequency of first cousin marriages contracted in G-B 1901–1952 can be estimated to be 1.9 per cent.

DISCUSSION

This incidence of first cousin marriages agrees with observations from rural areas in Götaland by Larsson and Sjögren (1954) and Svealand by Böök and Måwe (1955). Larsson and Sjögren observed an incidence of first cousin marriages of 2.6 ± 0.6 per cent for the native population and 2.3 ± 0.5 per cent for the resident popula-

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TABLE 1. POPULATION AND MIGRATION LOSSES OF G-B DURING THE PERIOD OF OBSERVATION, CALCULATED AS DIFFERENCES BETWEEN IN-MIGRATIONS AND OUT-MIGRATIONS

Period	Annual averages and standard errors		
	Population	Migration losses	
		Number	Per thousand of population
1901–1913	2,116 ± 16	23 ± 11	11 ± 5
1914–1926	1,991 ± 7	27 ± 8	13 ± 4
1927–1939	1,749 ± 31	35 ± 6	20 ± 3
1940–1952	1,344 ± 37	36 ± 6	26 ± 4

tion in the west coast district of AB:bo 1861–1920. Böök and Måwe studied a community on the Norwegian frontier and observed 7/570 first cousin marriages in 1925 and 7/535 in 1954, i.e. 1.2 and 1.3 per cent, respectively.

In both these studies, as in the present one, genealogic data were ascertained through official records. Larsson and Sjögren used as index cases parents of children born in AB:bo; Böök and Måwe investigated by census method existing marriages with both partners resident in Östmark; the present study concerned the marriages actually contracted in G-B. These different approaches, motivated by slightly differing aspects of the general problem, need impair neither the comparableness of the results nor their usefulness as preliminary estimates of first cousin marriage rates in wider rural areas.

The risks immanent in extrapolations to larger regions of kin mating rates observed in small districts could possibly be reduced by paying attention to substantial differences in the mobility of the populations in different regions. In his study of South Swedish birth-place fields, based on census figures of 1930, Bergsten (1951) observed that a broad region, including West Sweden and the county of Blekinge, was characterized by a tendency for people to remain in their birth community. A mainly East Swedish region was notable for a more mobile population and one zone, between this region and the Western one, was intermediary, as was the district where G-B is situated. Considering the influence of the community area on the percentage of residents born within the community, Bergsten observed, in that Western region of relatively stable population, a series of rural districts with decreasing excess of native residents. The district examined by Larsson and Sjögren was at the higher extreme of that series, the community of Böök and Måwe's investigation at the lower one. Actually one motive for Larsson and Sjögren's choice of this district for their investigation was that the annual influx of new residents was the lowest for any district in Sweden.

The rates of cousin marriages obtained by Böök and Måwe in a community they regarded as a geographic isolate, and by me in a community that was not such, were calculated on small numbers of positive observations and admit of no far-reaching conclusions as to the general frequency of first cousin marriages in rural Sweden. Extrapolations to the East Swedish belt of mobile population would perhaps be especially misleading; factors, limited to agricultural districts, and more potent than

differences in population mobility, might be responsible for the relatively high incidence of first cousin marriages in G-B. While an increased migration decreases the kin mating rate, as Larsson and Sjögren pointed out with regard to their observations, the present findings from a somewhat later period might evoke the question whether the decrease has really been rapid and substantial.

SUMMARY

In a South Swedish agricultural community with a decreasing, moderately mobile population, at least 10 (1.7 per cent) of 574 resident women married their first cousins during 1901–1952.

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"Linkage Studies" in Morphological Traits

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IT IS ALL TOO TRUE that the genetic structure determining traits of ordinary human morphology is as yet known in no case. This is in spite of such assumptions as have been made in the past (e.g. relative to eye color or skin color), and in contrast to traits of physiology (blood antigens) or developmental anomalies (brachydactyly). Of course, this is not surprising in a modern view of genetics; nonetheless it would certainly be valuable if any degree of linkage involving morphological traits could be found, as one means of analyzing their genetic bases (Brues, 1950).

Kloepfer (1946) made the first full scale attempt to find such evidence, recording sibling data for 19 traits, of which some were physiological (ABO, MN, PTC). He applied both a chi-square test and Penrose's graded character test (see below), and detected a number of possible linkages among the 171 combinations of traits allowed by his data. Taillard (1951) did a parallel study, though without using the graded character test, and found some support for certain of Kloepfer's results. The present paper reports another such study, testing 37 characters (666 possible combinations) recorded for approximately 75 male sibling pairs.

One principal point should be kept in mind as to the nature of these studies. In its only proper sense, linkage means the presence of two loci on the same chromosome pair, and the study of linkage implies a knowledge of the genes at the loci concerned. Now, for morphological, let alone quantitative, traits, this knowledge is exactly what is lacking; accordingly, "linkage studies" of the present sort, using unanalyzed traits rather than known gene pairs, are in a different category. They rest upon the assumption that, although precise knowledge is lacking, and although the traits are almost certainly in no case controlled by a single gene pair, there can be a gene pair involved having a sufficiently significant effect on the development of a trait so that linkage might be discovered among such influential gene pairs even at a stage at which they could not usefully be studied by other methods. The justification is, of course, that any stick will do to beat a dog when we remain so totally in the dark as to the genetics of normal morphology.

MATERIAL

The observations were made on pairs of brothers, drawn from the student body of the University of Wisconsin. All these men were of European ancestry, and native to Wisconsin; they ranged in age from 17 years 5 months to 30 years 10 months, and

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TABLE 1. LIST OF TRAITS

Relative linearity of body build
Lambdoid flattening
Hair form
Hair texture
Amount of hair on head
Amount of hair on second phalanx
Color of skin
Color of eyes
Thickness of eyebrows
Concurrency of eyebrows
Size of browridges
Size of glabella
Degree of forehead slope
Shape of nasal profile
Degree of nasion depression
Nose tip: thickness
Nose tip: elevation
Flare of nasal wings
Axis of nostrils
Thickness of lip
Degree of alveolar prognathism
Shape of chin
Direction of bite
Condition of teeth
Degree of crowding of teeth
Size of ear lobe
Degree of attachment of ear lobe
Amount of ear protrusion
Color of hair
Development of Darwin's point
Factor 1: general size
Factor 2: long bones
Factor 3: general cranial size
Factor 4: brain size
Factor 5: lateral facial-cranial development
Factor 6: facial length
Factor 7: ear size

the average difference between brothers was 2 years 8 months. Each pair was examined at the same time. Measurements were taken, these being the principal object of the investigation, and studies using this material have been published (Howells, 1953 and previous papers). Observations of a number of morphological traits were also made, those used in the present study being listed in table 1. It must be said that these observations were secondary to the work, not having the present analysis in view, and were therefore not made with any specially prepared precise method of scaling, or unusual exactness; nevertheless they were made according to standard anthroposcopic practice, especially of the Hooton school, by a competent and trained observer, working with both brothers at once. Ratings were made visually, using an objective scale only in the case of hair color; and scores were assigned according to a pre-established series of categories (e.g. in skin color or eye color) or a few grades

(e.g. "slight", "medium", "pronounced"). Since these ratings were made on both brothers of a pair simultaneously, they should reflect general likeness or unlikeness fairly well; that is, in the absence of absolute standards, differences between brothers would not be exaggerated by the shifting of the mental standards of the observer as to what "medium" might mean, a common hazard in such work. There are indications, however, that the observer did in fact change somewhat in his tendency, in some traits at least, to rate brothers as being alike; that is, there may have been a growing bias in the direction of scoring brothers in the same category where a difference was slight. At the same time, it is doubtful that any "halo effect" was present: that the observer in any way was anticipating the analysis herein performed. Furthermore, while this tendency on the part of the observer may have reduced the usefulness of the data, it is doubtful that the results were actually biassed, except in certain cases which will be noted.

Table 1 shows 7 "factors" among the traits used. These are numerical factor scores, derived from a factor analysis of the measurements (see Howells, 1951, 1953).

CHI-SQUARE TESTS

The sib-pair method of studying linkage, while not as efficient as the pedigree method, is far more available for exploration and general investigation. Neither the exact modes of inheritance nor the parental genotypes need be known or assumed, and the obstacles of slow generations and few offspring of a mating are circumvented. Continuous refinements of the sib-pair method since Penrose first introduced it (1935) have resulted in workable statistical techniques.

The primary analysis in this study consisted of testing all possible combinations of traits (666) by the chi-square test on 2 × 2 tables. For any trait, each sib pair was scored as "like" or "unlike" according as to whether or not there was a distinct disagreement of brothers in grade or character (for the factor scores, brothers were "like" if their difference was less than half the average pair-difference for that factor). These pair scores were punched on IBM cards and simple sorting produced fourfold tables for all combinations of traits. Examples are given in table 2, of which the first is the most important example of possible linkage found, and of which the second is a pair yielding evidence of linkage in Kloepfer's study, but not here.

In the absence of linkage (and other biassing factors) the frequencies of the four

TABLE 2. EXAMPLES OF ASSOCIATION IN 2 × 2 TABLES

	Darwin's point		
	Like	Unlike	Total
Nose tip, thickness			
Like	42	3	45
Unlike	18	11	29
Total	60	14	74
	Eye color		
Ear protrusion			
Like	35	30	65
Unlike	6	4	10
Total	41	34	75

possible classes in such a table should vary by sampling error about simple proportions to the marginal totals (as they do in the second example in table 2.) If the "like-like" and "unlike-unlike" classes are significantly increased, then there is a suggestion either of strong correlation between the traits (making brothers differ in both or neither), or of linkage. In table 3 are shown all the trait combinations yielding a χ^2 value of more than 3.84 (for which $P < .05$), totalling 36, of which 11 are

TABLE 3. SIGNIFICANT χ^2 VALUES OF 4-FOLD TABLES OF TRAITS (corrected for continuity when $E < 5$ for any cell)

Deviation in direction of linkage (excess of like-like and unlike-unlike associations)		Deviation *not* in direction of linkage (excess of like-unlike associations)
$P < .01$ ($\chi^2 > 6.63$)		
Size of browridges/Size of glabella	22.92	
Nose tip thickness/Darwin's point	11.25	
	8.68	Lip thickness/Factor 2: long bones
Skin color/Alveolar prognathism	8.55	
Glabella size/Factor 7: ear size	7.96	
Eyebrow thickness/Eyebrow concurrency	7.84	
Lambdoid flattening/Nasal profile	7.34	
Factor 1: general size/Factor 5: lateral cranial development	7.10	
Factor 4: brain size/Factor 5: lateral cranial development	7.10	
Factor 2: long bones/Hair texture	7.00	
Nasal profile/Condition of teeth	6.70	
$P > .01 < .05$ ($\chi^2 = 3.94$ to 6.63)		
Factor 1: general size/Factor 4: brain size	6.37	
Body build/Factor 4: brain size	5.67	
	5.48	Chin size/Factor 4: brain size
Factor 3: cranial size/Factor 5: lateral cranial development	5.29	
	5.18	Lambdoid flattening/Factor 7: ear size
Eye color/Tooth bite	5.12	
	5.11	Hair form/Nose tip elevation
	5.03	Nasion depression/Factor 1: general size
	4.94	Darwin's point/Factor 2: long bones
Hair form/Head hair, amount	4.87	
	4.87	Hair texture/Factor 6: face length
	4.78	Forehead slope/Factor 1: general size
Eyebrow concurrency/Nasion depression	4.77	
Ear lobe size/Ear lobe attachment	4.72	
	4.67	Hair form/Nasion depression
Hair texture/Factor 3: cranial size	4.50	
	4.50	Nasal wings flare/Factor 7: ear size
Factor 3: cranial size/Factor 4: brain size	4.44	
	4.39	Nose tip thickness/Factor 4: brain size
	4.39	Nose tip thickness/Factor 1: general size
Eyebrow thickness/Factor 4: brain size	4.37	
Browridge size/Nose tip elevation	4.27	
	4.23	Hair on 2nd phalanx/Lip thickness
	4.00	Factor 6: face length/Hair color
	3.90	Eyebrow thickness/Nasion depression

greater than 6.64, for which P < .01. This of course includes those tabulations in which the deviation is *not* in the direction suggesting linkage, i.e. those showing an excess of the like-unlike classes. Now, in 666 comparisons it might be expected that chance would yield χ^2 values greater than 3.84 in 666/20, or 33.3 cases, and greater than 6.64 in 6.66 cases. In the lower section of table 3, the generally equal numbers of trait pairs as between left and right columns (direction of linkage versus the opposite, of which the latter may be looked on as certainly chance deviations) suggests that *all* the deviations in this range (P > .01, < .05) from the expected are due to chance, as their total number suggests in the first place; and no evidence of linkage is afforded. At lower levels of P (first section of table 3), the result is slightly otherwise. Expectancy is for about 6 or 7 entries; 11 appear, of which 10 favor the possibility of linkage. The general conclusion is that, with correlation among traits still to be allowed for, actual evidence of linkage must be limited to extremely few cases out of the total tested.

GRADED CHARACTER TEST

Penrose (1938) suggested a test for linkage in graded characters which assumes determination by intermediate genes. In such a case, the estimation of linkage is independent of the gene frequencies, assuming the frequencies for the various sib pair differences to be normally distributed. Arbitrary grades (e.g. 0, 1, 2) are assigned to distinguishable variations, or presumed phenotypes, of the traits. (Grades of 0 and 1 may be assigned when a character has actual dominant or recessive states.) It is obvious that complex or multi-class characters like skin or hair color must be simplified as to the gradations used. The grade for the trait observed in one brother is subtracted from that observed for the other, care being taken that the same brother is always used for subtraction. The grade differences for each pair are then related to the corresponding differences for other traits; linkage of genes will increase the range of the covariance of their effects within sibships. The pertinent function is ϕ, which can be tested by its standard error, to obtain a "t" value, having the usual 5% level of significance at 1.96, and a 1% level at 2.56. This is shown as t_1 in table 4.

Because a constant association within individuals, i.e. a correlation, will raise the

TABLE 4. GRADED CHARACTER TESTS FOR LINKAGE

	t_1[1]	t_2[2]	χ^2[3]	N
	P < .001 (t_2 > 3.29)			
Nose tip thickness/Darwin's point	3.78	3.71	9.29	74
	P < .01 (t_2 > 2.58)			
Skin color/Alveolar prognathism	2.65	2.61	8.56	75
	P < .05 (t_2 > 1.96)			
Eyebrow thickness/Eyebrow concurrency	2.61	2.55	6.33	75
Size of browridges/Size of glabella	2.37	2.31	20.39	75
Lambdoid flattening/Nasal profile	2.26	2.22	7.34	73

[1] ϕ/σ
[2] $(\phi - r^2)/\sigma$
[3] Corrected in all cases for continuity.

mean value of the covariance, Penrose in a communication to Kloepfer (Kloepfer, 1946) suggested a method of adjusting the above function to eliminate the effect of correlation. This is done by subtracting r^2 from ϕ, r being the coefficient of correlation, calculated from the same data. This gives another estimate, $l_2 = (\phi - r^2)/\sigma$. (Formulae, etc. are given in Kloepfer's paper: or see Neel and Schull, 1954).

These tests were applied to all those trait pairs showing a significant chi-square in table 3 together with an association in the direction of linkage. The results are shown in table 4, listed in the order of magnitude of l_2, as the most stringent test. Chi-square is also shown once more, corrected for continuity throughout (since in many cases a cell has an expected value (E) of less than 10). It is evident from these refined results that the possible suggestions of linkage in table 3 must, with one exception, be regarded as the results of chance deviation or inherent correlation of traits. Values of l give the appearance of conforming to an expected curve of distribution. The "factor" traits were not scored suitably for this kind of test, but even as applied it did not indicate significant associations for them; the results are not shown. As for the pairs "eyebrow thickness/eyebrow concurrency" and "size of browridges/size of glabella", it is doubtful that the correlation computed, and used for correction, is as large as that actually existing; and in the case of the latter pair, the original data indicate a brother difference due to age, i.e. there is a small tendency for older brothers to have a constantly greater development of both of them, a special difference in the particular age period of this material which is not evident in other traits or measurements.

The one marked exception to all this is the association "nose tip thickness/Darwin's point". As in the case of χ^2, l_2 is highly significant, with a value distinctly larger than the next largest found, and in fact so well beyond the limits of the others generally (which give the impression of tailing off in expected fashion, especially when other smaller values, not shown, are considered), as to assume an order of magnitude by itself. That is to say, within the limits of the data, it gives the impression of standing apart as the one really suggestive case of possible linkage. The data, when examined further, do not suggest that correlation between the two traits is the actual factor responsible: coefficients of correlation and of contingency are approximately .20, and this has been corrected for in l_2. Finally, the two traits are such as might be presumed to have relatively simple genetic bases (though this is a presumption only); this should be a point of importance when linkage is being studied. The same cannot be said of all the traits considered, which is doubtless why so little of positive result is obtained.

DISCUSSION AND SUMMARY

In specific result, significant values of χ^2 and of Penrose's graded character test ϕ suggesting linkage are found for "nose tip thickness/Darwin's point" alone. Other values, even where significant at a 1% or 5% level, do not occur more frequently (among 666 comparisons) than expected by chance, and the next highest value of l_2, for "skin color/alveolar prognathism" is in any case barely significant at the 1% level.

In spite of the statistics in the case of brow ridges and glabella size, and eyebrow thickness and concurrency (table 4), it is difficult to see these pairs as independent

traits, either actually or in the eye of the observer, and thus as fully corrected for in the ϕ statistic (which in any event is not strongly significant in either case). Other associations, in table 3, such as those among "factors", must be disregarded because of the correlation among them or else because they do not appear to warrant consideration on a review of the data. It must be remembered, of course, that failure to find positive evidence of linkage does not preclude the existence of linkage, which might actually be found in fuller material more efficiently analyzed.

In previous investigations, Kloepfer and Taillard agreed in four instances of apparently significant linkage, viz.

ear size—ear flare
ear lobe attachment—finger length
ear size—PTC
red hair—strabismus

Otherwise, in some three fourths of the apparently significant linkages found by each, the one author could not support the other. The only check provided by our study among the four listed above is for ear size and flare, where ear size appears as a factor score (a linear combination of ear length and breadth), not as a visual observation. No evidence of linkage between this ear size and ear protrusion appears.

Six traits were studied by these two previous authors and by us, viz. ear protrusion, eye color, hair color, amount of hair on second phalanx, hair form, ear lobe attachment. Among these, Kloepfer found one instance of apparent linkage; the present authors found none, nor did Taillard. Kloepfer's case was a highly significant χ^2 and t score for "ear flare–eye color"; in our own study, the observed figures are close to those expected by chance (see table 2), with no indication of linkage.

Such disagreement does not vitiate the findings of Kloepfer and Taillard generally, since their data are more numerous, and also more carefully taken. Nevertheless some parallel sign of linkage might have been expected in our material, especially in the last case cited, and the failure to find it deepens the shadow over supposed linkages in morphological traits, including that indicated in this study.

Brues (1950), using a different method (testing of the variance) and including one numerical trait, a body build ratio, found evidence of linkage of the latter to both freckling and sex, via different chromosomes. Discovery of convincing linkages would be most welcome, as she points out, as an opening wedge into the genetics of physique, and it is to be hoped that the search will be prosecuted. At the moment, however, two things may be said. First, in the case of morphological traits which cannot be measured or categorized very exactly, the genetics may be too complex to allow ready detection of linkage by existing methods, even between the loci of major determinants of such features. Second, as to the anthropological side, it is ever more evident that the traits and categories which have been used to study ordinary variation are not close to expressing easily recognized genotypes, in spite of the guesswork as to modes of inheritance which has been so liberally applied to them in the past. It is to be hoped that geneticists will continue to provide improved techniques of analysis of traits; in the meanwhile, the anthropologists will probably have to take a

totally new look at the methods and categories they have been using to register physical traits before an area is created in which physique is convincingly reflected in genetics.

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Linkage Studies with Cystic Fibrosis of the Pancreas[1]

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INTRODUCTION

ANDERSEN AND HODGES (1946) concluded, from their analysis of the data provided by 31 families with at least two children in each, that cystic fibrosis of the pancreas is due to an autosomal recessive gene. Lowe, May and Reed (1949) analyzed the data derived from 95 families with at least two children in each and also concluded that cystic fibrosis is due to a recessive gene. Carter (1953) in a more detailed analysis of the data provided by 62 families in his study and the 126 families in the above mentioned studies confirmed this conclusion.

We have analyzed the data from 122 families with at least two children in each family and 19 families with only one child (the proband) in each family. Only one family resulted from a mating known to be consanguineous; the parents were third cousins. In these 141 families, there were 102 normal males and 103 normal females, and 96 affected males and 100 affected females. Obviously, sex is not a significant factor in determining liability to this disease. In our series, ascertainment was essentially minimal in that usually only one affected child in each family was independently ascertained. Table 1 presents a summary of these data, grouped by family size, number affected, and number ascertained. The proportion of affected offspring, computed by Weinberg's sib method using the observed ascertainment is 0.24 ± 0.03. Thus our data are also in agreement with the hypothesis that cystic fibrosis is due to a recessive gene, when the proper assumption concerning acertainment is made. Accordingly, it seemed reasonable to examine the possible linkage relations between this gene and the various blood group loci.

MATERIALS AND METHODS

The affected children were patients registered in the Nutrition Clinic of the Children's Hospital or seen as private patients of one of us (H.S.). Ten patients from the Connecticut Chapter of the Cystic Fibrosis Association were studied with the permission of their respective doctors. The diagnosis in each case was based on laboratory evidence of pancreatic enzyme deficiency, and in many cases it was con-

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TABLE 1. SUMMARY OF DATA FROM THE PEDIGREES OF PATIENTS WITH CYSTIC FIBROSIS OF THE PANCREAS

				Normal		Affected	
s*	r*	a*	n^*_{sra}	M	F	M	F
1	1	1	19	0	0	8	11
2	1	1	43	19	24	20	23
	2	1	5	0	0	5	5
	2	2	3	0	0	2	4
3	1	1	24	21	27	12	12
	2	1	8	3	5	11	5
	2	2	2	0	2	3	1
4	1	1	7	12	9	4	3
	2	1	11	11	11	9	13
	2	2	3	3	3	5	1
	3	1	4	3	1	3	9
5	1	1	4	9	7	2	2
	2	1	3	6	3	2	4
6	2	1	1	3	1	1	1
7	4	1	1	1	2	2	2
	4	2	1	2	1	2	2
11	1	1	1	6	4	1	0
12	6	2	1	3	3	4	2
Total			141	102	103	96	100

* s = number of offspring in family including the proband(s).
r = number of affected offspring in each family.
a = number of probands per family.
n_{sra} = number of families of size s, with r affected and a ascertained independently.

firmed by the finding of an abnormal concentration of sweat sodium and chloride in thermally induced sweat (see Shwachman, Leubner and Catzel 1955). The clinical picture, response to therapy, radiographic evidence, and, in a few instances, post mortem examinations, were consistent with the diagnosis. The patients' siblings were examined, and a medical history obtained.

The blood typing anti-sera that were used are listed in the Appendix. All families were tested for the ABO, Rh and MNS loci. Some were not tested for one or more of the other five loci. Anti-S and anti-C^w were not used in all cases (see Appendix).

The data were analyzed for the presence of linkage using C. A. B. Smith's (1954) modification of Finney's (1940) development of Fisher's (1935 a and b) μ functions. Smith's procedure, which is remarkably simple to use, has the great advantage of permitting the evaluation of linkage, separately, for each parent. As in Finney's method linkage is evaluated by computing a lambda score. Linkage is assumed if lambda is significantly greater than zero. A total of 70 families was examined in two consecutive series; the first series consisted of 29 families (families 1 through 29), the second of 41 families (families 30 through 70). (One family in the second series had to be omitted because the blood types showed that the affected child could not have been the offspring of the alleged father; father R_1R_2, mother R_1R_1 child R_1r. There was no ethnic difference in the composition of the two groups of families. All were white and most were of West European descent. The details of the blood groups of the two sets of families are presented in the Appendix.

TABLE 2. LAMBDA SCORES AND THEIR VARIANCES FOR LINKAGE BETWEEN CYSTIC FIBROSIS OF THE PANCREAS AND THE INDICATED BLOOD GROUPS

Locus	Mothers		Fathers		Families	
	Σλ	Σv*	Σλ	Σv	Σλ	Σv
ABO	−1.622	12.803	3.748	4.431	2.126	17.642
Rh	−0.557	22.081	−6.884	24.955	−7.441	47.496
K	1.063	1.491	0.063	0.836	1.126	2.453
Fy	3.439	7.535	−1.003	10.514	2.436	18.635
Jk	−0.457	0.874	−1.147	5.451	−1.604	7.869
P	2.277	1.237†	2.066	2.113	4.343	5.188†
Le	−1.486	5.402	0.135	4.782	−1.351	11.356

* v = variance.
† Significant at the 5 per cent level.

THE DATA

The lambda scores were either negative or did not differ significantly from zero for either parent in either series for any of the loci except the MNS. A summary of the lambda scores and the variances for the seven loci other than MNS is presented in Table 2. The amount of information is small for all the loci except ABO, Rh, and Fy. It is probable that close linkage with the Rh locus is excluded; the evidence is insufficient to justify a definite conclusion for any other locus. The data for the P locus indicate that it may be profitably tested further.

Eight of the twenty-nine families in the first series could not be used for linkage studies with the MNS locus, because both parents were homozygous for M or N and were either homozygous for one of the S alleles or were not tested with anti-S (see Appendix). Eight, of the 21 remaining families, provided information for the mother only, six for the father only, and seven for both parents. Thus 15 families provided information for the mother and 13 for the father. The lambda scores and the variances contributed by each of these 21 families are listed in Table 3A.

The Σλ for the fathers is negative; hence, there is no evidence for linkage between the MNS locus and the gene causing cystic fibrosis. On the other hand, the Σλ for the mothers is positive (10.970) and significantly different from zero; $\Sigma\lambda/\sqrt{\Sigma v} = 3.260$; $P < .0006$. This is strong evidence of linkage between the MNS locus and the gene causing cystic fibrosis. Furthermore, these data, in conjunction with those for the fathers, suggest that crossing over is more frequent in the human male than in the female, at least between these two loci. Differences between the sexes in the frequency of crossing over have been observed in other species including a mammal—the mouse (Gruneberg 1952). It is worth noting at this time, although we shall discuss this in more detail later, that there is no indication of heterogeneity within sex by the χ^2 test. There were one negative score, one zero score, and thirteen positive scores for the mothers, while there were six negative, one zero, and six positive scores for the fathers. The difference between the sexes in the frequency of positive and negative scores is significant at the 5 per cent level ($P = .042$).

Because we had a total of 16 tests of significance (two parents at each of eight loci), we felt that another series of families should be run to test again for the significance of the linkage between the MNS locus and the gene for cystic fibrosis.

TABLE 3. LAMBDA SCORES, AND THEIR VARIANCES, FOR LINKAGE BETWEEN THE MNS LOCUS AND THE GENE CAUSING CYSTIC FIBROSIS OF THE PANCREAS

A. FIRST SERIES

Family number	s	r	Smith's mating type	Mothers λ	Mothers v*	Mothers v'*	Fathers λ	Fathers v*
1	2	1	121	.333	.028	.028	.333	.028
2	3	1	22′	—	—	—	.778	.235
4	2	2	22′	—	—	—	−1.000	1.000
8	4	2	22	2.444	1.457	—	—	—
9	2	1	121	.333	.028	.028	.333	.028
10	2	1	121	.000	.028	.028	.000	.028
12	2	1	22	−.333	.111	—	—	—
13	2	1	22	.333	.111	—	—	—
14	5	1	22	.667	.518	—	—	—
16	2	1	22′	—	—	—	−.333	.111
18	4	2	22	.889	1.457	—	—	—
19	2	1	22′	—	—	—	.333	.111
21	2	1	22	.333	.111	—	—	—
22	4	3	22	2.000	3.333	—	—	—
23	3	2	22	.333	1.222	—	—	—
24	3	2	22′	—	—	—	−1.000	1.222
25	5	3	22′	—	—	—	−1.111	3.679
26	9	1	1111	.445	1.232	.000	−.443	1.232
27	4	1	121	.111	.092	.092	.111	.092
28	3	2	1111	1.684	1.240	.000	−.983	1.240
29	4	1	1111	1.398	.353	.000	.287	.353
Total				10.970	11.321	.176	−2.695	9.359

B. SECOND SERIES

30	2	1	22	.333	.111	—	—	—
31	4	2	22	−1.111	1.457	—	—	—
32	3	1	22′	—	—	—	−.111	.235
33	3	1	22	−.556	.235	—	—	—
34	2	1	121	.000	.028	.028	.000	.028
35	4	2	22′	—	—	—	.874	1.551
36	2	1	22′	—	—	—	.333	.111
37	2	1	22′	—	—	—	.333	.111
38	3	1	121	−.333	.059	.059	−.333	.059
39	3	1	121	.000	.059	.059	.000	.059
40	2	1	121	.000	.028	.028	.000	.028
42	2	1	121	.000	.028	.028	.000	.028
43	3	1	211	−.111	.235	.000	.300	.083
44	4	1	22	−.667	.370	—	—	—
45	2	1	22′	—	—	—	−.333	.111
46	3	1	22	.778	.235	—	—	—
47	2	1	211′	.063	.060	.000	.333	.111
48	3	1	121	.000	.059	.059	.000	.059
49	2	1	22	.333	.111	—	—	—
50	4	1	121	.000	.093	.093	.000	.093
51	3	1	1111	−.540	.224	.000	.095	.224
52	2	1	22	.333	.111	—	—	—
53	11	1	121	−.222	.417	.417	−.222	.417
54	2	1	31	.063	.023	.023	.063	.023
55	2	1	22	−.444	.099	—	—	—

TABLE 3. (*continued*)

B. SECOND SERIES—*Continued*

Family number	s	r	Smith's mating type	Mothers λ	Mothers v*	Mothers v'*	Fathers λ	Fathers v*
57	2	1	22	.333	.111	—	—	—
58	2	1	22′	—	—	—	.333	.111
59	2	1	22	−.333	.111	—	—	—
60	2	1	22′	—	—	—	−.333	.111
62	2	2	22′	—	—	—	1.000	1.000
63	2	1	22′	—	—	—	.222	.099
64	2	1	31	.063	.023	.023	.063	.023
65	3	1	22′	—	—	—	−.111	.235
66	4	2	22′	—	—	—	2.444	1.457
67	3	1	211	−.556	.235	.000	.745	.083
68	3	1	1111	−.111	.235	.000	−.556	.235
70	3	1	22′	—	—	—	.778	.235
Total				−2.685	4.757	.817	5.727	6.920

* v = variance; v′ = covariance.

The second series consisted of 41 families, of which four could not be used to test for linkage because both parents were homozygous at the MNS locus (3 cases), or because of doubtful paternity (1 case). A higher proportion of the families could be used in this series than in the first series, because almost all the families were tested with anti-S (see Appendix). Ten families yielded information for the mother only, 12 for the father only, and 15 for both parents; hence, 25 families provided information for the mothers and 27 for the fathers. The lambda scores and the variances contributed by each of the 37 families which provided information on linkage, for either or both parents, are presented in Table 3B. In contrast to the first series of families, this series does not offer any evidence for linkage in the mothers between the gene causing cystic fibrosis and the MNS blood group ($\Sigma\lambda = -2.685$). Even more surprisng is the observation that the lambda score for the fathers is positive (5.727), and that the probability that it is a sample from a population whose true value is zero is less than 0.015.

A summary of the data in each series, grouped by family size for each parent, separately and combined, is presented in Table 4 to permit tests for heterogeneity. The test for heterogeneity is based on the fact that D^2/v is distributed as χ^2, where D is the deviation from the expected value and v is the variance. For these data χ^2, with one degree of freedom, is approximately

$$\frac{\lambda_1^2}{v_1} + \frac{\lambda_2^2}{v_2} - \frac{(\sum\lambda)^2}{\sum v}.$$

(We are indebted to Dr. C. A. B. Smith for reminding us of this method of testing for heterogeneity.) The scores and variances of the smaller families were grouped, and compared with the grouped values for the larger families. The data were grouped to avoid very small samples. A summary of the various tests for heterogeneity is presented in Table 5. The first two sets of comparisons (1A and B, and 2A and B) indicate that, within each series, the data for each parent are homogeneous. Hence no

TABLE 4. LAMBDA SCORES AND VARIANCES FOR LINKAGE BETWEEN CYSTIC FIBROSIS AND THE MNS BLOOD GROUPS ARRANGED BY FAMILY SIZE

	Mothers			Fathers			Families	
s	n_s	λ	v	n_s	λ	v	λ(f)	v(f)
First Series								
2	6	0.999	0.417	6	−0.334	1.306	0.665	1.891
3	2	2.017	2.462	3	−1.205	2.697	0.812	5.159
4	5	6.842	6.692	2	0.398	0.445	7.240	7.321
5	1	0.667	0.518	1	−1.111	3.679	−0.444	4.197
9	1	0.445	1.232	1	−0.443	1.232	0.002	2.464
Total	15	10.970	11.321	13	−2.695	9.359	8.275	21.032
Second Series								
2	12	0.744	0.844	13	2.014	1.895	2.758	2.999
3	9	−1.429	1.576	10	0.617	1.507	−0.812	3.437
4	3	−1.778	1.920	3	3.318	3.101	1.540	5.207
11	1	−0.222	0.417	1	−0.222	0.417	−0.444	1.668
Total	25	−2.685	4.757	27	5.727	6.920	3.042	13.311

TABLE 5. SUMMARY OF THE TESTS FOR HETEROGENEITY

Comparisons	$x^2_{(1)}$	P
1. Series 1: Familes of 2 & 3 vs 4, 5 & 9		
A. Mothers	0.024	>0.8
B. Fathers	0.068	>0.7
2. Series 2: Familes of 2 & 3 vs 4 & 11		
A. Mothers	0.366	>0.5
B. Fathers	0.020	>0.8
3. Series 1 vs Series 2		
A. Mothers	7.876	≅0.004
B. Fathers	4.948	≅0.025
4. Mothers vs fathers		
A. Series 1	7.746	≅0.005
B. Series 2	5.463	≅0.02
C. Series 1 & 2 combined	.876	>0.3
5. Families		
A. Series 1: Families of 2 & 3 vs 4, 5, & 9	0.358	>0.5
B. Series 2: Families of 2 & 3 vs 4 & 11	0.068	≅0.8
C. Series 1 vs Series 2	0.222	>0.5

individual family or small group of families appears to have contributed unduly to the scores within each series. The situation is not the same, however, when we compare the total lambda score for the mothers in series one with that for the mothers in series two (comparison 3A in Table 5). The probability that the two series of mothers would have been obtained if they were samples from the same population is approximately 0.004. Similarly, the probability that the two series of fathers would have been obtained if they were samples from the same population is approximately 0.025.

We cannot account for the heterogeneity between the two samples. The known

differences between them are: (1) in the first series, an attempt was made to select larger families and families with two or more still-living affected children, the mean sizes of the usable families in series one and two were 3.3 and 2.8, and the mean number of affected children were 1.5 and 1.1, respectively, and (2) more of the families were tested with anti-S in the second series than in the first (8 out of 29 in the first series and 36 out of 41 in the second series). We see no reason why these differences between the two series should have introduced heterogeneity. These differences between the series cannot be the explanation for the heterogeneity between the mothers and fathers within each series; nevertheless, such statistical heterogeneity appears to exist (comparisons 4, Table 5).

The statistical techniques used to evaluate linkage are based on the theory of large samples. Such statistics are precise only as the sample size approaches infinity. Their distribution is not known for small samples; hence it is possible that the explanation for the heterogeneity of the data lies here. That is, the relatively small sample size and small amount of information may have led to spuriously significant scores.

The lambda score for a family, $\lambda(f)$ may be obtained by adding the scores for the mother and the father. The variance of these scores is the sum of the variances for the parents' scores plus twice the covariance (Smith 1954). A summary of the family scores grouped by family size is presented in Table 4. These scores and variances are almost identical with those which would have been obtained had Finney's (1940) procedure been used and Smith (1953) has shown that the total scores are asymptotically identical. When family scores are used, there is no evidence of heterogeneity either within or between the series (comparisons 5, Table 5). This observation suggests that the heterogeneity observed above is an accident of sampling and so is of no biological significance.

The sum of lambda for the first series is 1.80 times its standard error ($P \cong .036$) while that for the second series is 0.83 times its standard error ($P \cong .202$). The $\Sigma\lambda$ for the two series combined is 11.317, its variance is 34.343; hence $\Sigma\lambda$ is 1.93 times its standard error ($P \cong .027$).

In view of the ambiguity of the results and of the marginal significance or lack of significance of all lambda scores except that for the mothers in the first series, we must conclude that the evidence for linkage between the MNS blood groups and the gene causing cystic fibrosis of the pancreas is not convincing, but that further study seems warranted.

SUMMARY

Analysis of the data from 141 families confirmed earlier conclusions that cystic fibrosis of the pancreas is due to an autosomal recessive gene.

Linkage was tested between this gene and the ABO, Rh, MNS, K, Fy, Jk, Le, and P blood groups. C. A. B. Smith's method for testing linkage separately for each parent was used to analyze the data from 69 families.

No convincing evidence was found for linkage between any of the above blood groups and the gene causing cystic fibrosis. There is an indication that the large-sample theory upon which Smith's method is based may lead to spuriously significant results when dealing with samples of practical size.

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Appendix follows

Appendix. Family Blood Type Data

nl = normal, cf = cystic fibrosis of the pancreas, + = positive, − = negative, n = not done.

Family Number		Sex	Age	Anti-Sera																		
				A_1	A	B	C	c	C^w	D	E	e	M	N	S	K	k	Fy^a	Jk^a	Le^a	Le^b	P
1	Fa		42	n	−	−	+	+	n	+	−	n	+	+	n	−	n	n	n	n	n	n
	Mo		40	n	+	+	+	+	n	+	−	n	+	+	n	−	n	n	n	n	n	n
	1 nl	M	12	n	+	−	−	n	n	−	−	n	+	−	n	−	n	n	n	n	n	n
	2 cf	M	8	n	+	−	+	+	n	+	−	n	−	+	n	−	n	n	n	n	n	n
2	Fa		46	+	+	−	+	+	−	+	−	n	+	+	n	−	n	n	n	n	n	n
	Mo		36	+	+	−	+	−	+	+	−	n	−	+	n	+	n	n	n	n	n	n
	1 cf	M	6	+	+	−	+	+	+	+	−	n	+	+	n	+	n	n	n	n	n	n
	2 nl	F	4	+	+	−	+	−	+	+	−	n	−	+	n	+	n	n	n	n	n	n
	3 nl	M	2	+	+	−	+	+	+	+	−	n	−	+	n	−	n	n	n	n	n	n
3	Fa		36	n	+	+	+	+	−	+	−	n	−	+	n	+	n	n	n	n	n	n
	Mo		31	n	−	−	+	−	−	+	−	n	+	−	n	−	n	n	n	n	n	n
	1 nl	M	8	n	−	+	+	+	−	+	−	n	+	+	n	+	n	n	n	n	n	n
	2 cf	F	4	n	+	−	+	+	−	+	−	n	+	+	n	−	n	n	n	n	n	n
	3 nl	M	1	n	−	+	+	+	−	+	−	n	+	+	n	−	n	n	n	n	n	n
4	Fa		34	n	−	−	−	+	n	−	−	n	+	+	n	−	n	n	n	n	n	n
	Mo		31	n	+	−	−	+	n	−	−	n	+	−	n	−	n	n	n	n	n	n
	1 cf	M	3	n	−	−	−	+	n	−	−	n	+	−	n	−	n	n	n	n	n	n
	2 cf	F	1	n	−	−	−	+	n	−	−	n	+	+	n	−	n	n	n	n	n	n
5	Fa		26	n	+	−	+	+	n	+	−	n	−	+	n	−	n	n	n	n	n	n
	Mo		24	n	+	−	−	+	n	−	−	n	+	−	n	−	n	n	n	n	n	n
	1 cf	F	5	n	+	−	−	+	n	−	−	n	+	+	n	−	n	n	n	n	n	n
	2 cf	M	2	n	+	−	+	+	n	+	−	n	+	+	n	−	n	n	n	n	n	n
6	Fa		41	n	−	−	+	n	n	+	+	n	+	−	n	−	n	+	+	n	n	n
	Mo		36	n	−	−	+	n	n	+	+	n	+	−	n	−	n	−	+	n	n	n
	1 cf	M	8	n	−	−	−	n	n	+	+	n	+	−	n	−	n	+	−	n	n	n
	2 nl	M	7	n	−	−	−	n	n	+	+	n	+	−	n	−	n	−	+	n	n	n
7	Fa		26	+	+	−	−	n	n	+	+	n	+	−	n	−	n	n	n	n	n	n
	Mo		25	−	+	−	−	n	n	−	−	n	+	−	n	−	n	n	n	n	n	n
	1 cf	F	3	+	+	−	−	n	n	−	−	n	+	−	n	−	n	n	n	n	n	n
	2 nl	M	1	+	+	−	−	n	n	−	−	n	+	−	n	−	n	n	n	n	n	n
8	Fa		40	n	−	+	+	n	n	+	+	n	+	−	n	−	n	n	n	n	n	n
	Mo		36	n	+	+	−	n	n	−	−	n	+	+	n	−	n	n	n	n	n	n
	1 nl	F	11	n	+	+	−	n	n	+	+	n	+	−	n	−	n	n	n	n	n	n
	2 nl	F	7	n	+	+	−	n	n	+	+	n	+	−	n	−	n	n	n	n	n	n
	3 cf	M	5	n	+	−	−	n	n	+	+	n	+	+	n	−	n	n	n	n	n	n
	4 cf	M	4	n	−	+	+	n	n	+	−	n	+	+	n	−	n	n	n	n	n	n
9	Fa		32	n	−	+	+	−	n	+	−	n	+	+	n	−	n	n	n	n	n	n
	Mo		28	n	+	+	−	n	n	+	+	n	+	+	n	−	n	n	n	n	n	n
	1 nl	F	7	n	−	+	+	n	n	+	−	n	+	−	n	−	n	n	n	n	n	n
	2 cf	M	5	n	+	+	+	n	n	+	+	n	−	+	n	−	n	n	n	n	n	n
10	Fa		36	n	+	−	−	n	n	+	+	n	+	+	n	−	n	n	n	n	n	n
	Mo		34	n	+	−	+	−	n	+	−	n	+	+	n	−	n	n	n	n	n	n
	1 nl	M	9	n	+	−	+	n	n	+	+	n	+	+	n	−	n	n	n	n	n	n
	2 cf	F	3	n	−	−	+	n	n	+	−	n	+	+	n	−	n	n	n	n	n	n
11	Fa		27	n	−	+	−	n	n	−	−	n	+	−	n	−	n	n	n	n	n	n
	Mo		26	n	−	−	−	n	n	−	−	n	−	+	n	−	n	n	n	n	n	n
	1 nl	M	4	n	−	−	−	n	n	−	−	n	+	+	n	−	n	n	n	n	n	n
	2 cf	F	1	n	−	+	−	n	n	−	−	n	+	+	n	−	n	n	n	n	n	n

n = not done; nl = normal; cf = cystic fibrosis of pancreas

Family Number		Sex	Age	Anti-Sera																		
				A_1	A	B	C	c	C^w	D	E	e	M	N	S	K	k	Fy^a	Jk^a	Le^a	Le^b	P
12	Fa		32	n	−	−	+	−	−	+	−	n	+	−	n	−	n	+	+	n	n	+
	Mo		29	n	−	−	+	−	−	+	−	n	+	+	n	−	n	−	+	n	n	+
	1 cf	M	10	n	−	−	+	−	−	+	−	n	+	+	n	−	n	−	+	n	n	+
	2 nl	F	7	n	−	−	+	−	−	+	−	n	+	+	n	−	n	−	+	n	n	+
13	Fa		53	n	−	−	+	n	n	+	−	n	+	−	n	−	n	+	+	−	+	+
	Mo		37	n	−	−	−	n	n	+	+	+	+	+	n	−	n	+	+	−	+	+
	1 nl	F	7	n	−	−	−	n	n	+	+	n	+	+	n	−	n	+	+	−	+	+
	2 cf	M	6	n	−	−	+	n	n	+	+	n	+	−	n	−	n	+	+	−	+	+
14	Fa		37	n	−	+	+	−	−	+	−	n	+	−	n	−	n	n	n	n	n	n
	Mo		34	n	−	+	−	n	−	+	+	n	+	+	n	−	n	n	n	n	n	n
	1 nl	F	12	n	−	+	+	n	−	+	−	n	+	−	n	−	n	n	n	n	n	n
	2 nl	M	11	n	−	+	+	n	−	+	−	n	+	−	n	−	n	n	n	n	n	n
	3 nl	M	8	n	−	+	+	n	−	+	+	n	+	−	n	−	n	n	n	n	n	n
	4 cf	M	7	n	−	+	+	n	−	+	−	n	+	+	n	−	n	n	n	n	n	n
	5 nl	M	1	n	−	+	+	n	−	+	−	n	+	+	n	−	n	n	n	n	n	n
15	Fa		32	n	−	−	+	+	n	+	+	+	+	−	+	−	n	−	−	−	+	+
	Mo		30	−	+	−	−	+	n	+	+	+	+	−	+	−	n	+	+	−	−	+
	1 nl	M	8	−	+	−	+	+	n	+	+	+	+	−	+	−	n	+	+	+	−	+
	2 cf	F	7	−	+	−	−	+	n	+	+	+	+	−	+	−	n	+	+	−	+	+
	3 cf	F	6	n	−	−	+	+	n	+	−	+	+	−	+	−	n	+	+	+	−	+
	4 cf	M	4	n	−	−	−	+	n	+	+	+	+	−	+	−	n	+	+	−	+	+
16	Fa		24	n	+	−	−	+	n	+	+	+	+	+	n	−	n	+	+	+	−	n
	Mo		21	n	−	−	−	+	n	−	−	+	−	+	n	−	n	−	+	−	+	n
	1 cf	M	3	n	+	−	−	+	n	+	+	+	+	+	n	−	n	+	+	−	+	n
	2 nl	F	1	n	+	−	−	+	n	−	−	+	+	+	n	−	n	+	+	−	+	n
17	Fa		34	n	−	−	+	+	−	+	−	n	−	+	n	−	n	+	+	−	+	−
	Mo		28	n	−	−	+	+	−	+	−	n	+	−	n	−	n	+	+	+	−	+
	1 nl	F	4	n	−	−	+	+	−	+	−	n	+	+	n	−	n	+	+	+	−	+
	2 cf	M	3	n	−	−	+	+	−	+	−	n	+	+	n	−	n	+	+	−	+	+
18	Fa		36	+	+	−	+	−	+	+	−	n	−	+	−	−	n	+	+	+	−	n
	Mo		29	n	−	−	+	+	−	+	−	n	−	+	+	−	n	+	+	+	−	n
	1 nl	M	7	+	+	−	+	−	+	+	−	n	−	+	+	−	n	+	+	+	−	n
	2 cf	M	5	−	+	−	+	−	−	+	−	n	−	+	+	−	n	+	+	+	−	n
	*3 cf	M	3	+	+	−	+	+	+	+	−	n	−	+	+	−	n	+	+	+	−	n
	*4 nl	M	3	−	+	−	+	+	−	+	−	n	−	+	−	−	n	+	+	+	−	n
19	Fa		42	n	−	−	+	−	−	+	−	n	+	+	+	−	n	+	+	−	+	+
	Mo		43	n	−	−	+	+	−	+	−	n	−	+	−	−	n	+	+	+	−	+
	1 cf	F	9	n	−	−	+	+	−	+	−	n	+	+	+	−	n	+	+	−	+	+
	2 nl	M	5	n	−	−	+	−	−	+	−	n	−	+	−	−	n	+	+	−	+	+
20	Fa		50	n	−	−	+	+	n	+	+	n	−	+	−	+	n	+	+	−	+	+
	Mo		36	n	−	−	+	+	n	+	−	n	+	−	−	−	n	+	−	+	−	+
	1 nl	F	12	n	−	−	+	+	n	+	−	n	+	+	−	−	n	+	+	+	−	+
	2 cf	M	7	n	−	−	−	+	n	+	+	n	+	+	−	+	n	+	+	−	+	+
	3 nl	M	5	n	−	−	−	+	n	+	+	n	+	+	−	+	n	+	−	−	+	+
21	Fa		36	n	−	+	+	+	n	+	−	n	−	+	+	−	n	+	n	n	n	n
	Mo		34	n	−	−	+	+	n	+	−	n	+	+	+	+	n	+	n	n	n	n
	1 nl	F	10	n	−	+	+	−	n	+	−	n	−	+	+	−	n	+	n	n	n	n
	2 cf	F	5	n	−	−	+	−	n	+	−	n	+	+	+	+	n	+	n	n	n	n

* Fraternal twins.

Family Number		Sex	Age	Anti-Sera																		
				A_1	A	B	C	c	C^w	D	E	e	M	N	S	K	k	Fy^a	Jk^a	Le^a	Le^b	P
22	Fa		31	n	−	−	−	+	n	+	−	+	−	+	−	+	+	−	+	+	−	+
	Mo		31	n	−	−	−	+	n	−	+	+	+	+	+	+	+	+	+	−	+	+
	1 cf	F	7	n	−	−	−	+	n	−	−	+	+	+	+	+	−	+	+	+	−	+
	2 nl	M	5	n	−	−	−	+	n	−	+	+	+	+	+	+	−	+	+	+	−	+
	3 cf	M	4	n	−	−	−	+	n	+	+	−	+	+	+	+	−	−	+	−	+	+
	4 cf	M	3	n	−	−	−	+	n	−	−	+	+	+	+	+	−	−	+	+	−	+
24	Fa		35	+	+	−	+	−	−	+	−	n	−	+	n	−	n	−	+	−	+	−
	Mo		31	−	+	−	+	−	+	+	−	n	+	+	n	−	n	+	+	−	+	−
	1 cf	F	12	n	−	−	+	−	−	+	−	n	−	+	n	−	n	+	+	−	+	−
	2 cf	M	9	−	+	−	+	−	−	+	−	n	−	+	n	−	n	+	+	−	+	−
	3 nl	M	5	n	−	−	+	−	+	+	−	n	−	+	n	−	n	−	+	−	+	−
24	Fa		45	n	−	−	+	+	−	+	−	n	+	+	n	−	n	+	+	−	+	−
	Mo		46	n	−	−	+	+	+	+	−	n	+	−	n	−	n	−	+	−	+	−
	1 cf	F	20	n	−	−	+	−	+	+	−	n	+	+	n	−	n	+	+	−	+	−
	2 cf	M	17	n	−	−	+	+	−	+	−	n	+	−	n	−	n	−	−	−	+	−
	3 nl	M	13	n	−	−	+	+	+	+	−	n	+	−	n	−	n	+	+	−	+	−
25	Fa		36	n	−	−	+	+	n	+	−	n	+	+	−	−	n	+	+	−	+	+
	Mo		26	n	−	−	−	+	n	−	−	n	−	+	−	−	n	−	−	−	+	+
	1 nl	F	6	n	−	−	+	+	n	+	−	n	+	+	−	−	n	+	+	−	+	+
	2 cf	M	5	n	−	−	−	+	n	+	−	n	−	+	−	−	n	−	+	−	+	+
	3 cf	F	3	n	−	−	+	+	n	+	−	n	+	+	−	−	n	+	−	−	+	−
	4 cf	F	2	n	−	−	+	+	n	+	−	n	−	+	−	−	n	−	−	−	+	−
	5 nl	M	1	n	−	−	−	+	n	+	−	n	−	+	−	−	n	+	+	+	−	+
26	Fa		42	n	−	−	+	+	n	+	+	n	+	+	−	−	n	+	+	+	−	+
	Mo		39	n	−	−	+	+	n	+	−	n	+	+	+	−	n	−	−	−	+	+
	1 nl	M	13	n	−	−	+	−	n	+	−	n	−	+	−	−	n	−	+	−	+	+
	2 nl	M	11	n	−	−	−	+	n	+	+	n	+	+	+	−	n	−	+	−	+	+
	3 nl	M	9	n	−	−	−	+	n	+	+	n	+	+	−	−	n	+	−	+	−	+
	4 nl	M	8	n	−	−	−	+	n	+	+	n	−	+	−	−	n	+	−	−	+	+
	5 nl	M	7	n	−	−	+	+	n	+	+	n	+	−	+	−	n	−	+	+	−	−
	6 nl	F	6	n	−	−	+	−	n	+	−	n	+	−	+	−	n	−	−	−	+	+
	7 nl	M	5	n	−	−	+	−	n	+	−	n	+	−	+	−	n	−	−	−	+	+
	8 nl	M	2	n	−	−	−	+	n	+	+	n	+	+	+	−	n	+	+	+	−	+
	9 cf	F	1	n	−	−	−	+	n	+	+	n	+	+	−	−	n	+	−	−	+	+
27	Fa		35	n	−	−	+	−	n	+	−	n	+	+	+	−	n	−	+	+	−	−
	Mo		34	n	+	−	−	+	n	−	−	n	+	+	+	−	n	+	−	+	−	−
	1 nl	M	14	n	−	−	+	+	n	+	−	n	+	−	+	−	n	+	+	+	−	−
	2 nl	M	9	n	−	−	+	+	n	+	−	n	+	−	+	−	n	+	+	+	−	−
	3 nl	F	7	n	−	−	+	+	n	+	−	n	+	+	+	−	n	+	−	+	−	−
	4 cf	M	3	n	−	−	+	+	n	+	−	n	+	+	+	−	n	−	+	+	−	−
28	Fa		43	n	−	−	+	+	n	+	−	n	+	+	+	−	n	−	+	−	+	+
	Mo		39	n	−	−	−	+	n	−	−	n	+	+	−	−	n	+	+	−	+	+
	1 cf	M	11	n	−	−	−	+	n	−	−	n	+	+	+	−	n	−	+	−	+	−
	2 nl	F	7	n	−	−	−	+	n	−	−	n	+	+	−	−	n	+	+	−	+	+
	3 cf	F	4	n	−	−	+	+	n	+	−	n	−	+	−	−	n	+	+	−	+	−
29	Fa		39	n	−	−	+	−	n	+	−	n	+	+	+	−	n	+	+	−	+	+
	Mo		39	n	+	−	+	+	n	+	+	n	+	+	−	−	n	+	+	−	−	−
	1 nl	F	14	n	−	−	+	+	n	+	+	n	+	+	−	−	n	+	+	−	+	−
	2 nl	M	12	n	−	−	+	+	n	+	+	n	+	+	−	−	n	+	+	+	−	−
	3 nl	M	10	n	−	−	+	+	n	+	+	n	+	−	+	−	n	+	+	−	+	−
	4 cf	M	1	n	+	−	+	−	n	+	−	n	+	+	+	−	n	+	+	+	−	−

Family Number		Sex	Age	Anti-Sera																		
				A_1	A	B	C	c	C^w	D	E	e	M	N	S	K	k	Fy^a	Jk^a	Le^a	Le^b	P
30	Fa		36	n	−	−	−	+	n	−	−	n	−	+	−	−	n	+	+	+	−	+
	Mo		30	n	−	−	+	−	−	+	−	n	+	+	−	−	n	−	+	+	−	+
	1 nl	F	2	n	−	−	+	+	−	+	−	n	+	+	−	−	n	+	+	+	−	+
	2 cf	F	1	n	−	−	+	+	−	+	−	n	−	+	−	−	n	+	+	+	−	+
31	Fa		32	n	−	−	−	+	n	+	+	−	+	−	+	−	n	−	+	−	+	+
	Mo		30	+	+	−	+	+	n	+	−	n	+	+	+	−	n	+	+	−	−	+
	1 nl	M	5	n	−	−	+	+	n	+	+	n	+	−	+	−	n	+	−	−	+	+
	2 cf	M	4	+	+	−	+	+	n	+	+	+	+	+	+	−	n	+	+	−	−	+
	3 cf	F	3	+	+	−	+	+	n	+	+	n	+	−	+	−	n	+	+	−	−	+
	4 nl	M	1	+	+	−	−	+	n	+	+	n	+	+	+	−	n	+	−	−	−	+
32	Fa		36	n	−	−	+	+	n	+	+	n	+	+	−	−	n	−	+	+	−	+
	Mo		35	n	−	−	+	+	n	+	+	n	+	−	+	−	n	+	+	−	+	−
	1 nl	M	9	n	−	−	−	+	n	+	+	n	+	+	+	−	n	+	+	+	−	−
	2 cf	F	6	n	−	−	+	−	n	+	−	n	+	+	+	−	n	+	+	−	+	+
	3 nl	M	3	n	−	−	−	+	n	+	+	n	+	−	+	−	n	+	+	−	+	+
33	Fa		35	n	+	−	+	−	−	+	−	n	−	+	+	−	n	−	+	−	−	−
	Mo		30	n	−	−	+	−	−	+	−	n	+	+	+	+	n	+	n	−	+	+
	1 nl	M	6	n	+	−	+	−	−	+	−	n	+	+	+	−	n	+	+	−	−	+
	2 cf	F	5	n	−	−	+	−	−	+	−	n	+	+	+	−	n	+	+	−	+	−
	3 nl	F	2	n	+	−	+	−	−	+	−	n	+	+	+	−	n	+	+	−	+	+
34	Fa		34	n	+	−	−	+	n	+	+	+	+	+	+	−	n	−	+	n	n	n
	Mo		33	n	+	+	+	+	n	+	+	+	+	+	+	−	n	+	+	n	n	n
	1 cf	F	7	n	−	+	−	+	n	+	+	+	+	+	+	−	n	−	+	n	n	n
	2 nl	M	4	n	+	+	−	+	n	+	+	+	−	+	+	−	n	+	+	n	n	n
35	Fa		39	n	−	−	+	−	n	+	−	n	+	−	+	−	n	+	+	+	−	+
	Mo		40	n	+	−	+	+	n	+	−	n	+	−	−	−	n	+	+	+	−	+
	1 nl	F	14	n	−	−	+	−	n	+	−	n	+	−	−	−	n	−	+	+	−	+
	2 cf	F	7	n	+	−	+	+	n	+	−	n	+	−	−	−	n	+	+	+	−	+
	3 nl	F	2	n	+	−	+	+	n	+	−	n	+	−	+	−	n	+	+	+	−	+
	4 cf	F	1	n	+	−	+	+	n	+	−	n	+	−	−	−	n	+	+	+	−	+
36	Fa		29	+	+	−	−	+	n	−	−	n	+	+	−	−	n	−	+	−	−	+
	Mo		22	+	+	−	+	+	n	+	+	n	+	−	+	−	n	−	+	+	−	+
	1 cf	F	2	+	+	−	−	+	n	+	+	n	+	+	+	−	n	−	+	+	−	+
	2 nl	M	1	+	+	−	+	+	n	+	−	n	+	−	+	−	n	−	+	+	−	+
37	Fa		38	n	+	−	+	+	n	+	−	n	+	+	−	−	n	+	−	−	+	+
	Mo		34	n	−	−	+	−	n	+	−	n	+	−	+	−	n	+	+	−	+	+
	1 nl	F	7	n	+	−	+	+	n	+	−	n	+	−	+	−	n	+	+	−	+	+
	2 cf	F	3	n	−	−	+	+	n	+	−	n	+	+	+	−	n	+	+	−	+	+
38	Fa		41	+	+	−	−	+	n	−	−	n	+	+	n	−	n	−	−	−	−	+
	Mo		38	n	−	−	+	+	n	+	+	n	+	+	n	−	n	+	+	+	−	+
	1 nl	F	13	+	+	−	−	+	n	+	+	n	−	+	n	−	n	+	−	+	−	+
	2 nl	M	7	n	−	−	+	+	n	+	−	n	+	+	n	−	n	+	−	−	+	+
	3 cf	F	2	+	+	−	+	+	n	+	−	n	−	+	n	−	n	+	−	−	−	+
39	Fa		27	n	−	+	+	−	n	+	−	n	+	+	+	−	n	−	+	n	n	n
	Mo		26	n	−	−	+	+	n	+	+	n	+	+	+	−	n	+	+	n	n	+
	1 nl	F	5	n	−	−	+	+	n	+	+	n	+	+	+	−	n	−	+	n	n	+
	2 nl	M	3	n	−	−	+	+	n	+	+	n	+	+	+	−	n	−	+	n	n	+
	3 cf	M	1	n	−	−	+	+	n	+	+	n	+	−	+	−	n	+	+	n	n	+

Family Number		Sex	Age	Anti-Sera																		
				A_1	A	B	C	c	C^w	D	E	e	M	N	S	K	k	Fy^a	Jk^a	Le^a	Le^b	P
40	Fa		40	n	+	−	−	+	n	−	+	+	+	+	+	−	+	−	n	−	−	+
	Mo		40	n	+	−	+	+	n	+	+	+	+	+	+	+	+	−	n	−	+	+
	1 cf	F	13	n	−	−	+	+	n	+	+	+	+	−	+	+	+	−	n	−	+	+
	2 nl	M	8	n	−	−	−	+	n	+	+	−	+	+	+	+	+	−	n	−	+	+
41	Fa		29	n	−	−	−	+	n	−	−	n	−	+	−	+	n	−	+	−	+	+
	Mo		28	n	−	−	−	+	n	+	+	+	+	−	+	−	n	+	−	−	+	+
	1 cf	M	5	n	−	−	−	+	n	+	+	+	+	+	+	+	n	−	+	−	+	+
	2 nl	F	4	n	−	−	−	+	n	+	+	n	+	+	+	+	n	+	+	−	+	+
	3 nl	M	3	n	−	−	−	+	n	+	+	n	+	+	+	−	n	+	+	−	+	+
42	Fa		63	n	−	−	+	+	n	+	−	n	+	+	+	+	+	−	+	−	+	−
	Mo		26	+	+	−	+	−	n	+	−	n	+	+	+	+	+	+	−	−	−	+
	1 nl	F	5	−	+	−	+	−	n	+	−	n	+	−	+	+	+	+	+	−	+	+
	2 cf	F	2	−	+	−	+	−	n	+	−	n	+	+	+	+	+	−	+	−	+	+
43	Fa		31	n	−	−	−	+	n	+	+	n	+	−	+	−	n	+	+	−	+	+
	Mo		32	n	−	−	+	+	n	+	+	n	+	+	+	−	n	+	+	+	−	−
	1 cf	F	7	n	−	−	+	+	n	+	−	n	+	−	+	−	n	+	+	+	−	+
	2 nl	M	6	n	−	−	+	+	n	+	+	n	+	−	−	−	n	+	−	−	+	−
	3 nl	F	4	n	−	−	−	+	n	+	+	−	+	+	+	−	n	+	+	−	+	−
44	Fa		44	n	−	−	+	+	n	+	−	n	−	+	−	−	n	+	n	+	−	+
	Mo		43	n	−	−	−	+	n	−	−	n	+	+	+	−	n	+	n	−	+	+
	1 nl	M	15	n	−	−	+	+	n	+	−	n	−	+	+	−	n	+	n	−	+	−
	2 nl	F	14	n	−	−	+	+	n	+	−	n	−	+	+	−	n	−	n	−	+	+
	3 nl	M	8	n	−	−	+	+	n	+	−	n	−	+	+	−	n	+	n	−	+	+
	4 cf	F	6	n	−	−	+	+	n	+	−	n	−	+	+	−	n	+	n	−	+	−
45	Fa		31	−	+	−	−	+	n	+	+	n	+	+	+	−	n	+	−	+	−	+
	Mo		31	n	−	−	+	+	n	+	−	n	−	+	−	−	n	+	+	−	+	+
	1 cf	M	2	−	+	−	−	+	n	+	+	n	+	+	+	−	n	+	−	+	−	+
	2 nl	M	1	−	+	−	−	+	n	−	−	n	+	+	+	−	n	+	+	−	+	+
46	Fa		35	−	+	−	+	+	n	+	−	n	+	−	+	−	n	+	−	+	−	+
	Mo		34	+	+	−	+	−	n	+	−	n	+	+	+	−	n	−	+	+	−	+
	1 nl	F	8	+	+	−	+	−	n	+	−	n	+	−	+	−	n	+	+	+	−	+
	2 nl	M	7	+	+	−	+	+	n	+	−	n	+	−	+	−	n	+	+	+	−	+
	3 cf	F	3	+	+	−	+	−	n	+	−	n	+	+	+	−	n	+	+	+	−	+
47	Fa		29	n	−	−	+	+	n	+	−	n	+	+	+	+	n	+	n	−	+	+
	Mo		28	n	−	−	+	−	n	+	−	n	+	−	+	−	n	+	n	−	+	+
	1 nl	M	3	n	−	−	+	+	n	+	−	n	+	−	+	+	n	+	n	−	+	+
	2 cf	F	1	n	−	−	+	+	n	+	−	n	+	+	−	+	n	+	n	−	+	+
48	Fa		47	n	−	−	+	+	n	+	−	n	+	+	n	−	n	−	−	n	n	+
	Mo		44	n	+	−	+	+	n	+	−	n	+	+	n	−	n	+	+	n	n	+
	1 nl	F	15	n	−	−	−	+	n	−	−	n	+	+	n	−	n	+	+	n	n	+
	2 nl	F	12	n	+	−	−	+	n	−	−	n	+	+	n	−	n	−	+	n	n	+
	3 cf	M	4	n	+	−	+	+	n	+	−	n	+	+	n	−	n	−	+	n	n	+
49	Fa		31	n	+	−	+	−	n	+	−	n	+	−	n	−	n	−	+	n	n	−
	Mo		29	n	+	−	+	+	n	−	−	n	+	+	n	−	n	−	+	n	n	+
	1 nl	F	7	n	−	−	+	−	n	+	−	n	+	+	n	−	n	−	+	n	n	−
	2 cf	M	3	n	+	−	+	−	n	+	−	n	+	−	n	−	n	−	+	n	n	−
50	Fa		39	n	+	−	+	−	n	+	−	n	+	+	n	−	n	+	+	−	+	+
	Mo		39	n	+	−	+	+	n	+	+	n	+	+	n	−	n	+	+	−	−	+
	1 nl	F	14	n	−	−	+	−	n	+	−	n	+	−	n	−	n	+	+	+	−	+

Family Number		Sex	Age	Anti-Sera																		
				A_1	A	B	C	c	C^w	D	E	e	M	N	S	K	k	Fy^a	Jk^a	Le^a	Le^b	P
	2 nl	F	12	n	+	−	+	+	n	+	+	n	+	+	n	−	n	+	+	−	−	+
	3 nl	F	8	n	−	−	+	+	n	+	+	n	+	+	n	−	n	+	+	+	−	+
	4 cf	M	4	n	+	−	+	+	n	+	+	n	+	+	n	−	n	+	+	−	+	−
51	Fa		25	n	−	+	+	+	n	+	−	n	+	+	+	−	n	+	−	n	n	n
	Mo		21	n	+	−	−	+	n	−	−	n	+	+	−	−	n	+	+	n	n	n
	1 cf	F	3	n	+	+	+	+	n	+	−	n	+	+	−	−	n	+	+	n	n	n
	2 nl	M	2	n	−	+	−	+	n	−	−	n	+	−	+	−	n	+	+	n	n	n
	3 nl	M	1	n	+	+	−	+	n	−	−	n	+	+	−	−	n	+	+	n	n	n
52	Fa		39	n	+	−	+	+	n	+	−	n	−	+	−	−	n	+	−	−	+	n
	Mo		39	n	−	−	+	−	n	+	−	n	+	+	+	−	n	+	+	+	−	n
	1 cf	M	2	n	−	−	+	−	n	+	−	n	+	+	+	−	n	+	−	+	−	n
	2 nl	F	1	n	−	−	+	−	n	+	−	n	−	+	−	−	n	+	+	−	+	n
53	Fa		48	n	−	−	+	+	n	+	−	n	+	+	n	−	n	+	+	−	+	+
	Mo		46	n	−	−	−	+	n	+	+	n	+	+	n	−	n	−	+	+	−	+
	1 nl	M	27	n	−	−	−	+	n	+	+	n	+	+	n	−	n	+	−	−	+	+
	2 nl	M	25	n	−	−	+	+	n	+	+	n	−	+	n	−	n	−	+	−	+	+
	3 nl	F	23	n	−	−	+	+	n	+	−	n	+	+	n	−	n	−	+	−	+	+
	4 nl	M	19	n	−	−	−	+	n	+	+	n	+	+	n	−	n	−	−	−	+	−
	5 nl	M	16	n	−	−	+	+	n	+	+	n	+	+	n	−	n	−	+	−	+	+
	6 nl	F	14	n	−	−	+	+	n	+	+	n	+	+	n	−	n	−	+	−	+	+
	7 nl	M	12	n	−	−	−	+	n	−	−	n	−	+	n	−	n	−	+	−	+	+
	8 nl	F	10	n	−	−	+	+	n	+	+	n	+	−	n	−	n	−	+	−	+	+
	9 nl	M	8	n	−	−	+	+	n	+	+	n	+	+	n	−	n	−	+	−	+	−
	10 cf	M	6	n	−	−	−	+	n	+	+	n	+	+	n	−	n	−	+	−	+	+
	11 nl	F	5	n	−	−	+	+	n	+	+	n	−	+	n	−	n	−	+	−	+	+
54	Fa		38	n	+	−	−	+	n	−	−	n	+	−	+	−	n	+	−	n	n	n
	Mo		33	n	+	−	+	+	n	+	−	n	−	+	+	−	n	+	+	n	n	n
	1 nl	M	3	n	+	−	+	+	n	+	−	n	+	+	−	−	n	+	−	n	n	n
	2 cf	F	2	n	+	−	−	+	n	−	−	n	+	+	+	−	n	+	+	n	n	n
55	Fa		38	n	+	−	+	−	n	+	−	n	−	+	−	+	n	+	n	n	n	n
	Mo		36	n	−	−	+	+	n	+	+	n	−	+	+	+	n	+	n	n	n	n
	1 nl	F	12	n	−	−	+	−	n	+	−	n	−	+	−	−	n	+	n	n	n	n
	2 cf	M	8	n	+	−	+	−	n	+	−	n	−	+	−	+	n	+	n	n	n	n
57*	Fa		33	n	−	−	+	+	n	+	−	n	+	−	+	−	n	−	+	n	n	n
	Mo		30	n	+	−	−	+	n	+	+	n	+	+	−	−	n	+	+	n	n	n
	1 cf	M	7	n	−	−	−	+	n	−	−	n	+	−	+	−	n	+	+	n	n	n
	2 nl	F	6	n	−	−	+	+	n	+	−	n	+	+	+	−	n	+	−	n	n	n
58	Fa		44	n	−	−	−	+	n	+	+	+	+	+	−	−	n	−	+	n	n	n
	Mo		43	n	−	−	+	−	n	+	−	n	+	−	+	−	n	+	+	n	n	n
	1 nl	M	13	n	−	−	+	+	n	+	+	n	+	−	+	−	n	+	+	n	n	n
	2 cf	M	10	n	−	−	+	+	n	+	+	n	+	+	+	−	n	+	+	n	n	n
59	Fa		36	n	−	−	+	+	n	+	−	n	−	+	−	−	n	−	+	n	n	n
	Mo		40	n	+	−	+	−	n	+	−	n	+	+	+	−	n	+	+	n	n	n
	1 cf	M	12	n	−	−	+	+	n	+	−	n	−	+	−	−	n	−	+	n	n	n
	2 nl	F	6	n	−	−	+	−	n	+	−	n	−	+	−	−	n	+	+	n	n	n
60	Fa		28	n	+	−	+	+	n	+	+	n	+	+	−	−	n	+	−	n	n	n
	Mo		26	n	−	−	+	−	n	+	−	n	−	+	+	−	n	−	+	n	n	n

* Family 56 omitted because of questionable paternity, see text.

Family Number		Sex	Age	Anti-Sera																		
				A_1	A	B	C	c	C^w	D	E	e	M	N	S	K	k	Fy^a	Jk^a	Le^a	Le^b	P
	1 cf	F	6	n	−	−	+	−	n	+	−	n	−	+	+	−	n	+	+	n	n	n
	2 nl	M	1	n	+	−	+	−	n	+	−	n	−	+	+	−	n	+	+	n	n	n
61	Fa		38	n	−	−	+	−	n	+	−	n	+	−	+	−	n	−	+	n	n	n
	Mo		35	n	−	−	+	−	n	+	−	n	−	+	+	−	n	−	+	n	n	n
	1 cf	F	12	n	−	−	+	−	n	+	−	n	+	+	+	−	n	−	−	n	n	n
	2 nl	M	7	n	−	−	+	−	n	+	−	n	+	+	+	−	n	−	−	n	n	n
62	Fa		25	n	−	+	+	−	n	+	−	n	+	+	−	−	n	−	n	n	n	n
	Mo		26	n	−	−	+	+	n	+	−	n	+	−	−	+	n	−	n	n	n	n
	1 cf	F	2	n	−	−	+	+	n	+	−	n	+	+	−	+	n	−	n	n	n	n
	2 cf	F	1	n	−	−	+	−	n	+	−	n	+	+	−	−	n	−	n	n	n	n
63	Fa		31	n	−	−	+	+	n	+	−	n	+	−	+	−	n	+	+	n	n	n
	Mo		34	n	+	−	−	+	n	−	−	n	−	+	−	−	n	−	+	n	n	n
	1 nl	M	2	n	−	−	−	+	n	−	−	n	+	+	−	−	n	+	−	n	n	n
	2 cf	M	1	n	+	−	−	+	n	−	−	n	+	+	+	−	n	+	+	n	n	n
64	Fa		39	n	−	+	+	−	n	+	−	n	+	+	+	−	n	+	+	n	n	n
	Mo		34	n	−	+	+	+	n	+	+	n	+	+	+	−	n	+	+	n	n	n
	1 cf	M	11	n	−	−	+	+	n	+	+	n	+	+	−	−	n	+	+	n	n	n
	2 nl	F	10	n	−	+	+	−	n	+	−	n	+	+	+	−	n	+	+	n	n	n
65	Fa		29	n	+	−	+	−	n	+	−	n	+	+	+	−	n	+	+	n	n	n
	Mo		28	n	−	−	+	+	n	+	+	n	+	−	+	−	n	−	+	n	n	n
	1 nl	F	7	n	+	−	+	−	n	+	−	n	+	−	+	−	n	−	+	n	n	n
	2 nl	F	3	n	−	−	+	−	n	+	−	n	+	+	+	−	n	+	+	n	n	n
	3 cf	M	1	n	−	−	+	−	n	+	−	n	+	−	+	−	n	−	−	n	n	n
66	Fa		39	n	−	−	+	+	n	+	−	n	+	+	+	−	n	+	+	n	n	n
	Mo		32	n	+	−	+	−	n	+	−	n	+	−	+	−	n	−	+	n	n	n
	1 nl	M	10	n	+	−	+	+	n	+	−	n	+	+	+	−	n	+	+	n	n	n
	2 cf	M	6	n	−	−	+	+	n	+	−	n	+	−	+	−	n	+	+	n	n	n
	3 nl	M	4	n	+	−	+	+	n	+	−	n	+	+	+	−	n	−	+	n	n	n
	4 cf	F	1	n	+	−	+	−	n	+	−	n	+	−	+	−	n	+	+	n	n	n
67	Fa		36	n	−	−	−	+	n	−	−	n	−	+	+	−	n	+	−	n	n	n
	Mo		35	n	+	−	−	+	n	−	−	n	+	+	+	−	n	+	+	n	n	n
	1 cf	F	10	n	+	−	−	+	n	−	−	n	−	+	+	−	n	+	−	n	n	n
	2 nl	M	8	n	+	−	−	+	n	−	−	n	−	+	−	−	n	+	−	n	n	n
	3 nl	M	3	n	−	−	−	+	n	−	−	n	−	+	−	−	n	+	+	n	n	n
68	Fa		33	n	−	+	+	−	n	+	−	n	+	+	−	−	n	+	−	n	n	n
	Mo		26	n	+	+	+	+	n	+	−	n	+	+	+	−	n	−	+	n	n	n
	1 cf	M	7	n	+	+	+	−	n	+	−	n	+	+	+	−	n	−	+	n	n	n
	2 nl	F	5	n	+	+	+	−	n	+	−	n	−	+	−	−	n	+	+	n	n	n
	3 nl	F	4	n	+	+	+	−	n	+	−	n	+	+	+	−	n	+	+	n	n	n
69	Fa		30	n	−	−	+	+	n	+	−	n	+	−	−	−	n	+	+	−	+	−
	Mo		28	n	−	−	−	+	n	−	−	n	−	+	−	−	n	+	+	−	+	−
	1 nl	F	6	n	−	−	−	+	n	−	−	n	+	+	−	−	n	+	+	−	+	−
	2 cf	M	5	n	−	−	+	+	n	+	−	n	+	+	−	−	n	+	+	−	+	−
70	Fa		37	n	−	+	−	+	n	−	−	n	+	+	+	−	n	−	+	n	n	n
	Mo		36	n	−	−	+	+	n	+	+	n	+	−	+	−	n	−	+	n	n	n
	1 nl	M	6	n	−	+	−	+	n	+	+	n	+	+	+	−	n	−	+	n	n	n
	2 cf	M	5	n	−	+	+	+	n	+	−	n	+	−	+	−	n	−	+	n	n	n
	3 nl	F	2	n	−	+	−	+	n	+	+	n	+	+	+	−	n	−	+	n	n	n

Sequential Test for Linkage Between Cystic Fibrosis of the Pancreas and the MNS Locus[1]

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INTRODUCTION

DATA FOR LINKAGE between the recessive gene causing cystic fibrosis of the pancreas and several blood group loci have been analysed by Steinberg, Shwachman, Allen, and Dooley (1956) using C. A. B. Smith's (1954) modification of Fisher's scores. They concluded (a) that there was no convincing evidence for linkage between cystic fibrosis and any of the blood group loci tested, and (b) that Smith's scores, based on large sample theory, may lead to spuriously significant results when applied to samples of practical size.

We present a reanalysis of the data for the MNS locus, using the sequential test for the detection of linkage (Morton, 1955 and 1956), to illustrate the use of the method on a specific set of data, and to introduce two new equations which make the method applicable to mating types not included in Morton's original paper.

EXPLANATION AND ILLUSTRATION OF THE METHOD

In brief, and ignoring the statistical arguments justifying the method, the sequential test for linkage consists (1) of determining for each family a score z, which is the logarithm of the quotient obtained by dividing the probability (p_1) that the family would have occurred with an assumed frequency of recombination $\theta_1(\theta_1 < 0.5)$ by the probability (p_0) that the family would have occurred if there were no linkage, $\theta = 0.5$; and (2) of comparing the sum of the scores for successive families with predetermined constants to decide whether linkage is present.

The z score may be positive or negative. It is positive if the probability of obtaining the family is greater on the assumption of linkage ($\theta = \theta_1$) than it is on the assumption of no linkage ($\theta = 0.5$); it is negative if the reverse is true. The z scores of successive families are totaled algebraically. When the sum of z exceeds three, it is concluded that linkage is present. On the other hand, when the sum of z becomes less than minus two, it is concluded that recombination is greater than θ_1. So long as the sum of z remains between these extremes, insufficient information is available to reach a decision and further sampling is required. No assumption and no approximation is made concerning the normality of the distribution of z; hence, large sample theory is not involved.

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The probability of detecting linkage when the true value of recombination is equal to the assumed value of θ_1 is 0.99 and increases rapidly as the true value becomes less than θ_1 (Morton, 1955). The probability of detecting linkage, when the true value of recombination is greater than the assumed value of θ_1, is always less than 0.99, and approaches .001 or less as θ approaches 0.5. When $\theta = 0.5$ (i.e., no linkage) the probability of z exceeding three before becoming less than two is less than 0.001. It might seem desirable, from the foregoing, to select a large value of θ_1, say 0.4, to test against the hypothesis of no linkage ($\theta_0 = 0.5$). In this way the probability of detecting linkage would be at least 0.99 for all true values of recombination equal to or less than 0.4. Unfortunately there is a penalty attached to such a choice. On the average, the smaller the difference between θ_1 and θ_0, the larger the sample needed to reach a decision. There is, however, a simple way out of this dilemma. In the linkage test z is computed for the largest value of θ_1 which might be expected to reach significance in a practical sample. For linkage of a rare recessive with MNS, with fewer than 50 units of information expected, a reasonable choice would be $\theta_1 = .10$ (Morton, 1955, tables 2 and 9). To carry out large-sample heterogeneity tests, z is computed for a series of values of θ_1. This is not difficult, because tables have been published for values of z corresponding to a series of values of θ_1, and to various family constellations (Morton, 1955). Furthermore, direct calculation of the z scores is not onerous.

The families which can be used for linkage analyses at the MNS locus are listed and classified into mating types according to Smith's scheme in table 3 of the paper by Steinberg and colleagues (1956). All families involve matings between heterozygotes for cystic fibrosis; the differential among the families therefore resides in the MNS locus.

Families classified as 22 (or 22′) in Smith's method correspond to Morton's mating types 9 or 11, Cfcf Ss × Cfcf ss tested with anti-S only and Cfcf MN × Cfcf MM, respectively, for example. In other words, for the test locus they are equivalent to a backcross which involves dominance or one which does not involve dominance, respectively. In the latter cross the parents' genotypes with regard to the test factor can be determined directly; hence, no correction is necessary in this method, just as none is in Smith's method. In the former mating type (type 9, involving dominance), the genotype of the heterozygous parent is recognized only if a recessive child occurs. A correction is needed for the omission of those families with a heterozygous parent which have not produced a recessive child.

Mating types 9 and 11 are scored as z_2 (Morton, 1955, page 293). The score can be read from a table (*ibid.*, table 11, page 306) after the offspring have been classified with respect to the test and marker genes. We reproduce the MN data for family 8 (Steinberg and colleagues, 1956, appendix) to illustrate the scoring of families of mating type 11.

	Cystic Fibrosis	MN
Fa	−	MM
Mo	−	MN
1	−	MM
2	−	MM
3	+	MN
4	+	MN

Each child must fall into one of four phenotypic categories as follows (Morton, 1955, Table 5):

	a	b	c	d
Morton's symbols	GT_1	gT_1	GT_1T_2	gT_1T_2
Equivalents for family 8	−MM	+MM	−MN	+MN

Clearly the first two children are "a" and the second two are "d"; family size, "s", is 4. The values for z_2, for the various values of θ_1, listed opposite family 8 in table 3B of this paper were found in table 11 of Morton's 1955 paper, under s = 4, a = 2, d = 2. It will be recalled that θ_1 is the recombination value being tested against the hypothesis of no linkage, i.e., $\theta_0 = 0.5$. The values for $\theta_1 = 0$ were computed directly from the equation for z_2 (Morton, 1955, page 293).

The scoring of families of mating type 9 is the same as for mating type 11 except that, as mentioned above, a correction factor is necessary. The correction needed depends upon the method of ascertainment of families (Morton, 1955). In the present case selection for the main factor (cystic fibrosis) was via the affected children and ascertainment was incomplete. Selection for the test factor (MNS locus), within the sample of families, was complete and of the type classified as truncate (Bailey, 1951, Morton, 1955); that is, the distribution of anti-S negative children among the families is a binomial distribution with the first term (none anti-S negative) missing. The correction is e_2, and may be read from table 15, page 314 of Morton's paper after classifying the children into the number normal (s_1) and the number affected (s_2). We illustrate this procedure with the data from family 18 (Steinberg and colleagues, 1956) which is reproduced below.

	Cystic Fibrosis	S
Fa	−	−
Mo	−	+
1	−	+
2	+	+
3	+	+
4	−	−

Here again the children may be distributed among four phenotypic categories.

	a	b	c	d
Morton's symbols	GT	gT	Gt	gt
Equivalents for family 18	−+	++	−−	+−

The z scores (except for $\theta_1 = 0$) were read at s = 4, a = 1, b = 2, and c = 1 (line 2, page 307, Morton, 1955); the corrections (e_2) were read at s = 4, $s_1 = s_2 = 2$ in table 15, page 314 of Morton's paper. These scores are entered in table 3B opposite family 18.

Families of Smith mating type 31 in this series of families are as follows: Cfcf Ss × CfCf Ss (tested with anti-S only, families 54 and 64 in table 4C) and are equivalent to Morton's mating type 13. They are scored as z_3 with correction e_3.

Note that in mating types 9 and 11 only one parent is heterozygous for the test factor, but in mating type 13 both parents are heterozygous for the test factor. Mating types 9 and 11 therefore contribute to the score of the heterozygous parent, while in mating type 13 the linkage scores of the parents are confounded and cannot be listed

separately. Mating type 13 contributes to the family scores but not to the individual parental score.

Families of Smith mating type 121 in this series are: Cfcf MN × Cfcf MN (see Tables 3C and 4C for examples). They are classified as mating type 14. As in mating type 13, both parents are doubly heterozygous, but the matings differ in that there is no dominance in the test factor in mating type 14. The parents' genotypes, relative to MN, may be determined directly; therefore, no correction is needed. Families of mating type 14 are scored as z_4 (Table 7, page 294, Morton, 1955). The scores must be computed from the equation, because tables have not been published.

Two other mating types are encountered among the data of Steinberg and his colleagues for which z-score equations have not been published, namely Smith mating types 211 (or 211′) and 1111 with both parents heterozygous for the main factor which involves dominance.

MATING TYPES 17 AND 18 AND THEIR z SCORES, z_6 AND z_7

Table 1 presents a summary of the derivation of z_6 for mating type 17, Smith's mating type 211 (or 211′), with both parents heterozygous for the main factor which involves dominance. The frequencies of the various types of progeny may be derived from the usual checkerboard diagram. When there is no linkage ($\theta = \frac{1}{2}$) the progeny occur in the ratio of 6/16 a: 2/16 b: 3/16 c, etc., (table 1). Then, assuming no linkage the probability (p_0) that s off-spring would be distributed among the several phenotypes in the frequencies a, b, c, d, e, and f respectively, is

$$\frac{s!}{a!b!c!d!e!f!}\left[\frac{6^a 2^b 3^c 1^d 3^e 1^f}{16^s}\right]$$

where $s = a + b + c + d + e + f$,

$$= K\left[\frac{2^{a+b}3^{a+c+e}}{4^{2s}}\right], \qquad \text{where } K = \frac{s!}{a!b!c!d!e!f!}$$

TABLE 1: MATINGS SCORED WITH z_6. DOUBLE INTERCROSS WITH DOMINANCE IN ONE FACTOR AND THREE ALLELES OF THE ABO TYPE IN THE OTHER (MATING TYPE 17)

Parental Genotype	Frequency of Progeny of Indicated Phenotypes						
Gg T_1t_2 × Gg T_1t	GT_1	gT_1	GT_2	gT_2	GT_1T_2	gT_1T_2	Common divisor
	a	b	c	d	e	f	
Coupling × Coupling	$2-\theta$	θ	$\theta(2-\theta)$	$(1-\theta)^2$	$1-\theta+\theta^2$	$\theta(1-\theta)$	4
Coupling × Repulsion	$2-\theta$	θ	$1-\theta+\theta^2$	$\theta(1-\theta)$	$\theta(2-\theta)$	$(1-\theta)^2$	4
Repulsion × Coupling	$1+\theta$	$1-\theta$	$1-\theta+\theta^2$	$\theta(1-\theta)$	$1-\theta^2$	θ^2	4
Repulsion × Repulsion	$1+\theta$	$1-\theta$	$1-\theta^2$	θ^2	$1-\theta+\theta^2$	$\theta(1-\theta)$	4
$\theta = \frac{1}{2}$	6	2	3	1	3	1	16

$$z_6 = \log \frac{4^s - 1}{2^{a+b}3^{a+c+e}}\,[(2-\theta)^{a+c}\theta^{b+c+f}(1-\theta)^{2d+f}(1-\theta+\theta^2)^e + (2-\theta)^{a+c}\theta^{b+d+e}(1-\theta+\theta^2)^e(1-\theta)^{d+2f} + (1+\theta)^a(1-\theta)^{b+d}(1-\theta+\theta^2)^c\theta^{d+2f}(1-\theta^2)^e + (1+\theta)^a(1-\theta)^{b+f}(1-\theta^2)^c\theta^{2d+f}(1-\theta+\theta^2)^e]$$

The probability that the s progeny would be distributed among these phenotypes in the observed frequencies if $\theta < \frac{1}{2}$ is also derived from table 1. The assumed linked genes in each parent may be in coupling or repulsion; hence, there are four ways in which mating type 17 may occur: coupling × coupling, coupling × repulsion, etc. Each of these is expected to occur with equal frequency. Because they are mutually exclusive, the average probability for mating type 17, assuming linkage, is 1/4 of the sum of the probabilities of each of the four ways mating type 17 may occur. The probability that the observed distribution of offspring results from the type 17 coupling × coupling mating is, from row 1 of table 1,

$$\frac{s!}{a!b!c!d!e!f!}\left[\frac{(2-\theta)^{a+e}\theta^{b+e+f}(1-\theta)^{2d+f}(1-\theta+\theta^2)^e}{4^s}\right]$$

Let this equal $K[A/4^s]$.

The probabilities for the remaining ways that mating type 17 may occur are derived from table 1 in exactly the same way.

Let these equal $K[B/4^s]$, $K[C/4^s]$, and $K[D/4^s]$, respectively, then the probability (p_1) that the progeny arose from a mating of type 17 in which linkage was present is

$$\tfrac{1}{4}\left[K\left(\frac{A}{4^s}\right)+K\left(\frac{B}{4^s}\right)+K\left(\frac{C}{4^s}\right)+K\left(\frac{D}{4^s}\right)\right]=\frac{K}{4^{s+1}}[A+B+C+D].$$

Therefore,

$$z_6=\log\frac{p_1}{p_0}=\log\frac{4^{2s}}{K2^{a+b}3^{a+c+e}}\left[\frac{K}{4^{s+1}}\right][A+B+C+D]$$

$$=\frac{4^{s-1}}{2^{a+b}3^{a+c+e}}[A+B+C+D].$$

The type example, for the test locus, of a mating of this type is AB × AO, the offspring being ½A (AA and AO), ¼B, and ¼AB. An example for the MNS locus is MS/Ns × MS/Ms (tested with anti-S only), the offspring being ½M(S+), MSMS and MSMs not being distinguished, ¼ MN(S+), and ¼ MN(S−).

Family 43 (Steinberg and colleagues, 1956) which is reproduced below, is of this type.

	Cystic Fibrosis	MN	S
Fa	−	MM	+
Mo	−	MN	+
1	+	MM	+
2	−	MM	−
3	−	MN	+

The first child is of phenotype d, the second, e, and the third, a (see Table 1). These values are substituted in z_6 to derive the scores entered in table 4C. A correction is needed because the parents' genotypes with respect to S were ascertained from the phenotypes of the children. The mating with respect to S alone is of type 13 which is scored with z_3; hence, the correction is e_3 (Table 7, page 314, Morton, 1955), with $s = 3$, $s_1 = 2$, and $s_2 = 1$. These values are entered in table 4C directly beneath the z scores.

If only MN is considered the family may be scored as mating type 11 for the

TABLE 2. MATINGS SCORED WITH Z_7. DOUBLE INTERCROSS WITH DOMINANCE IN ONE FACTOR AND ALL FOUR ALLELES OF THE OTHER INDIVIDUALLY IDENTIFIABLE IN THE PROGENY (MATING TYPE 18)

Parental Genotype	Frequency of Progeny of Indicated Phenotypes								
Gg T_1T_5 × Gg T_5T_6	GT_1T_5 a	gT_1T_5 b	GT_5T_5 c	gT_5T_5 d	GT_5T_6 e	gT_5T_6 f	GT_5T_6 g	gT_5T_6 h	common divisor
Coupling × Coupling	$1-\theta^2$	θ^2	$1-\theta+\theta^2$	$\theta(1-\theta)$	$1-\theta+\theta^2$	$\theta(1-\theta)$	$\theta(2-\theta)$	$(1-\theta)^2$	4
Coupling × Repulsion	$1-\theta+\theta^2$	$\theta(1-\theta)$	$\theta(2-\theta)$	$(1-\theta)^2$	$1-\theta^2$	θ^2	$1-\theta+\theta^2$	$\theta(1-\theta)$	4
Repulsion × Coupling	$1-\theta+\theta^2$	$\theta(1-\theta)$	$1-\theta^2$	θ^2	$\theta(2-\theta)$	$(1-\theta)^2$	$1-\theta+\theta^2$	$\theta(1-\theta)$	4
Repulsion × Repulsion	$\theta(2-\theta)$	$(1-\theta)^2$	$1-\theta+\theta^2$	$\theta(1-\theta)$	$1-\theta+\theta^2$	$\theta(1-\theta)$	$1-\theta^2$	θ^2	4
$\theta = \frac{1}{2}$	3	1	3	1	3	1	3	1	16

$$z_7 = \text{Log}\frac{4^{a-1}}{3^{a+c+e+g}}\left[(1-\theta^2)^{a+b+d+f+g}(1-\theta+\theta^2)^{c+e}(1-\theta)^{d+f+2h}(2-\theta)^g + (1-\theta+\theta^2)^{a+2g}(1-\theta)^{b+e+2f+h}(2-\theta)^c(1-\theta^2)^e + (1-\theta+\theta^2)^{a+2g}(1-\theta)^{b+2f+h}(1-\theta^2)^c(2-\theta)^e + \theta^{a+d+f+2h}(2-\theta)^g(1-\theta)^{2b+d+f}(1-\theta+\theta^2)^{c+e}(1-\theta^2)^g\right]$$

mother. This was done and the score is entered in table 4B. Furthermore, the family may be scored as mating type 9 for the father if we score only the M(S+) and M(S−) offspring. This score is entered in table 4A. This method of treating the family is less efficient than scoring it as z_6 but it does permit a separation of the parental scores and is useful when, as in this analysis, the scores for the mothers are to be compared with those for the fathers.

Table 2 presents a summary of the derivation of z_7 for scoring families of mating type 18, the equivalent of Smith's mating type 1111. The type example for the test locus is AO × BO, the offspring being A, B, O, and AB. In each case there is no doubt as to which gene the child has inherited from a given parent. An example for the MNS locus is MSNs × MsNs the offspring being MN(S+), M(S+), MN(S−), N(S−).

Family 28 is a mating of this type; the data are reproduced below:

	Cystic Fibrosis	MN	L(A)
Fa	−	MN	+
Mo	−	MN	−
1	+	MN	+
2	−	MN	−
3	+	NN	−

The first child is of phenotype f, the second, c, and the third, h (Table 2). When these values are substituted in equation z_7 the scores entered in table 3C result. A correction is required because the father's genotype was identified via his progeny. If we consider S only, the mating is of type 9 for the father; hence, the correction to z_7, is e_2. These values, read from table 15 in Morton's paper, are also entered in table 3C. We have already mentioned that the family may be treated as mating type 9 for the

TABLE 3. z SCORES FOR SERIES 1

A. FATHER DOUBLY HETEROZYGOUS

Family No.	Mating Type		z at indicated values of θ 0	.05	.10	.20	.30	.40
2	11			.2122	.1754	.1072	.0509	.0133
4	11		−∞	−.7212	−.4437	−.1938	−.0757	−.0177
16	11			−.1367	−.1042	−.0555	−.0238	−.0058
19	11			.1038	.0840	.0492	.0226	.0058
24	11			−.7212	−.4437	−.1938	−.0757	−.0177
25	11			−.7622	−.4757	−.2115	−.0835	−.0197
26*	11			−.1638	−.1281	−.0709	−.0312	−.0077
28*	9			−.7212	−.4437	−.1938	−.0757	−.0177
		e		.0171	.0134	.0075	.0033	.0008
29*	9			.0628	.0519	.0315	.0148	.0038
		e		−.0160	−.0126	−.0070	−.0031	−.0008
Totals								
(a)	With 26, 28 and 29		−∞	−2.8464	−1.7270	−0.7309	−0.2771	−0.0634
(b)	Without 26, 28 and 29		−∞	−2.0253	−1.2079	−0.4982	−0.1852	−0.0398

* Scored also as confounded, i.e. z_7.

TABLE 3—*Continued*

B. MOTHER DOUBLY HETEROZYGOUS

Family No.	Mating Type		z at indicated values of θ 0	.05	.10	.20	.30	.40
8	11		.5509	.4847	.4166	.2775	.1442	.0406
12	11		−.1761	−.1367	−.1042	−.0555	−.0238	−.0058
13	11		.1249	.1038	.0840	.0492	.0226	.0058
14	11		.1987	.1712	.1434	.0895	.0431	.0114
18	9		.2499	.2167	.1828	.1158	.0567	.0151
		e	−.0032	−.0031	−.0028	−.0019	−.0009	−.0003
21	11		.1249	.1038	.0840	.0492	.0226	.0058
22	11		.4260	.3804	.3311	.2245	.1178	.0332
23	11		.1249	.1038	.0840	.0492	.0226	.0058
26*	9		.0964	.0893	.0794	.0540	.0276	.0075
		e	−.0008	−.0005	−.0002	.0000	.0000	.0000
28*	11		.4260	.3711	.3153	.2041	.1027	.0280
29*	11		.3748	.3231	.2715	.1717	.0843	.0226
Totals								
(a)	With 26, 28 and 29		2.5173	2.2076	1.8849	1.2273	0.6195	0.1697
(b)	Without 26, 28 and 29		1.6209	1.4246	1.2189	0.7975	0.4049	0.1116

* Scored also as confounded, i.e. z_7.

C. BOTH PARENTS DOUBLY HETEROZYGOUS

Family No.	Mating Type	z		z at indicated values of θ_1 0	.05	.10	.20	.30	.40
1	14	4			.1210	.1106	.0780	.0406	.0112
9	14	4			.1210	.1106	.0780	.0406	.0112
10	14	4			−.1072	−.0638	−.0192	−.0034	−.0002
26*	18	7		−∞	−.1611	−.0129	.0241	.0077	.0006
			e		−.0005	−.0002	—	—	—
27	14	4			.0694	.0595	.0356	.0158	.0039
28*	18	7			−.3529	−.1284	.0103	.0269	.0103
			e		.0171	.0134	.0075	.0033	.0008
29*	18	7			.3303	.2837	.1869	.0951	.0261
			e		−.0160	−.0126	−.0070	−.0031	−.0008
Totals				−∞	0.0211	0.3599	0.3942	0.2235	0.0631

* See scores for mothers, and for fathers.

father if only S is considered. This was done and the appropriate z_2 (b = 1, c = 1, d = 1) and e_2 (s = 3, s_1 = 1, s_2 = 2) scores have been entered in table 3A.

Family 28 may also be considered as mating type 11 for the mother by treating all offspring who have inherited her M as dominant and those who have inherited her N as recessive. The appropriate z_2 (d = 2, a = 1) scores have been entered in table 3B.

DISCUSSION

The z scores, and where necessary the e scores, for each family in series 1 and series 2 are listed in tables 3 and 4, respectively. Families 26, 28, and 29 in table 3 and 43, 47, 51, 76, and 68 in table 4 were scored as z_2 for each parent separately, and also as z_6 or z_7 for both parents doubly heterozygous. The "a" totals for tables 3A, 3B, 4A,

and 4B include these families, and may be used to examine the data for the mothers and fathers separately. The "b" totals in these tables exclude these families and may be used to compute the total family scores. The various totals are summarized in table 5.

It will be recalled that analysis by Smith's method, of the data for the families in series 1 which were scored for the mothers, indicated that linkage was present ($p < 0.0006$ that these families were a sample with no linkage). The highest total z score (table 5A) reached for the mothers of series 1 is 2.52 at $\theta_1 = 0$, and the lowest is more than minus two. Hence the data do not permit a decision concerning linkage. This is in sharp contrast with the conclusion reached using Smith's method.

The data for series-1 fathers are sufficient to exclude recombination equal to or less than five per cent [$\Sigma z_{(\theta_1=0.05)} = -2.85$]. The z-score totals for values of θ_1 greater than 0.05 do not permit a decision. Hence, while close linkage is excluded, loose linkage is

TABLE 4. z SCORES FOR SERIES 2

A. FATHER DOUBLY HETEROZYGOUS

Family No.	Mating Type		z at indicated values of θ_1 0	.05	.10	.20	.30	.40
32	11		−.0512	−.0410	−.0320	−.0177	−.0078	−.0019
35	9		.2499	.2167	.1828	.1158	.0567	.0151
		e	−.0032	−.0031	−.0028	−.0019	−.0009	−.0003
36	11		.1249	.1038	.0840	.0492	.0226	.0058
37	11		.1249	.1038	.0840	.0492	.0226	.0058
43*	9		.1249	.1038	.0840	.0492	.0226	.0058
		e	−.0332	−.0271	−.0215	−.0122	−.0055	−.0014
45	11		−.1761	−.1367	−.1042	−.0555	−.0238	−.0058
47*	11		.1249	.1038	.0840	.0492	.0226	.0058
51†	9		−.0512	−.0410	−.0320	−.0177	−.0078	−.0019
		e	−.0332	−.0271	−.0215	−.0122	−.0055	−.0014
58	11		.1249	.1038	.0840	.0492	.0226	.0058
60	11		−.1761	−.1367	−.1042	−.0555	−.0238	−.0058
62	11		.3010	.2577	.2148	.1335	.0645	.0170
63	9		.1249	.1038	.0840	.0492	.0226	.0058
		e	−.0458	−.0374	−.0298	−.0170	−.0077	−.0019
65	11		−.0512	−.0410	−.0320	−.0177	−.0078	−.0019
66	11		.5509	.4847	.4166	.2775	.1442	.0406
67*	9		.2499	.2122	.1754	.1072	.0509	.0133
		e	−.0332	−.0271	−.0215	−.0122	−.0055	−.0014
68*	9		−.0512	−.0410	−.0320	−.0177	−.0078	−.0019
		e	−.0332	−.0271	−.0215	−.0122	−.0055	−.0014
70	11		.2499	.2122	.1754	.1072	.0509	.0133
Totals								
(a)	With 43, 47, 51, 67 and 68		1.6122	1.4200	1.2140	0.7869	0.3934	0.1071
(b)	Without 43, 47, 51, 67 and 68		1.3477	1.1906	1.0206	0.6655	0.3349	0.0916

* Scored also as z_4.

† Scored also as z_7.

TABLE 4—*Continued*

B. MOTHERS DOUBLY HETEROZYGOUS

Family No.	Mating Type		z at indicated values of θ_1 0	.05	.10	.20	.30	.40
30	11			.1038	.0840	.0492	.0226	.0058
31	11		−∞	−.7622	−.4757	−.2115	−.0835	−.0197
33	11			−.2596	−.1908	−.0969	−.0404	−.0098
43*	11			−.0410	−.0320	−.0177	−.0078	−.0019
44	11			−.3608	−.2532	−.1219	−.0494	−.0118
46	11			.2122	.1754	.1072	.0509	.0133
49	11			.1038	.0840	.0492	.0226	.0058
51†	11			−.2596	−.1908	−.0969	−.0404	−.0098
52	11			.1038	.0840	.0492	.0226	.0058
55	9			−.1367	−.1042	−.0555	−.0238	−.0058
		e		−.0374	−.0298	−.0170	−.0077	−.0019
57	11			.1038	.0840	.0492	.0226	.0058
59	11			−.1367	−.1042	−.0555	−.0238	−.0058
67*	11			−.2596	−.1908	−.0969	−.0404	−.0098
68†	9			−.0410	−.0320	−.0177	−.0078	−.0019
		e		−.0271	−.0215	−.0122	−.0055	−.0014
Totals								
(a)	With 43, 51, 67 and 68		−∞	−1.6943	−1.1136	−0.4957	−0.1892	−0.0431
(b)	Without 43, 51, 67 and 68		−∞	−1.0660	−0.6465	−0.2543	−0.0873	−0.0183

* Scored also as z_6.

† Scored also as z_7.

C. BOTH PARENTS DOUBLY HETEROZYGOUS

Family No.	Mating Type	z		z at indicated vales of θ_1 0	.05	.10	.20	.30	.40
34	14	4			.0859	.0556	.0184	.0037	.0002
38	14	4		−∞	−.6174	−.3597	−.1446	−.0531	−.0120
39	14	4			.1994	.1100	.0417	.0086	.0005
40	14	4			.0859	.0556	.0184	.0037	.0002
42	14	4			.0859	.0556	.0184	.0037	.0002
43*	17	6			.1888	.1366	.0614	.0111	.0042
			e_3		−.0470	−.0348	−.0173	−.0069	−.0016
47*	17	6			.1038	.0840	.0492	.0226	.0058
			e_3		−.0447	−.0336	−.0172	−.0071	−.0017
48	14	4			−.1969	−.1121	−.0324	−.0062	−.0004
50	14	4			−.1732	−.0840	−.0255	−.0050	−.0003
51*	18	7			−.6174	−.3597	−.1446	−.0531	−.0120
			e_2		−.0271	−.0215	−.0122	−.0055	−.0014
53	14	4			−.8053	−.3139	−.1335	−.0436	−.0085
54	13	3			.0979	.0747	.0392	.0164	.0039
			e_2		−.0447	−.0336	−.0172	−.0071	−.0017
64	13	3			.0979	.0747	.0392	.0164	.0039
			e_3		−.0447	−.0336	−.0172	−.0071	−.0017
67*	17	6			.1888	.1366	.0614	.0111	.0042
			e_3		−.0470	−.0348	−.0173	−.0069	−.0016
68*	18	7			−.6174	−.3597	−.1446	−.0531	−.0120
			e_2		−.0271	−.0215	−.0122	−.0055	−.0014
Totals				−∞	−2.1756	−1.0191	−0.3885	−0.1629	−0.0332

* See scores for mothers, and for fathers.

not. This conclusion is in agreement with that of the previous analysis, but is more precise because the λ score permitted only the statement that evidence for linkage is not significant.

The data for series 2 exclude absolute linkage in the mothers but are not sufficient to reach a conclusion for any of the other values of θ_1. The data for the fathers do not permit any conclusion concerning linkage for any value of θ_1 including $\theta_1 = 0$.

Table 6 presents a summary of the maximum values ($\hat{Z}$) attained by Z, the sum of z. These maximum values were derived by plotting the values of the sum of z against θ, and reading the maximum value from the graph (Morton, 1955 and 1956). In no instance does $\hat{Z}$ reach a value of three; hence in no instance is there significant evidence for linkage. The marked differences between the scores for mothers and fathers within each series, and between the scores for a parent of a given sex in series 1 and series 2 are very apparent. This is in agreement with the previous analysis. Chi-square analysis of the z scores [$\chi^2_{(1)} = 2(\log_e 10)\ (\Sigma\hat{z}_i - \hat{Z})$, where $\hat{z}_i$, $\hat{Z}$ are the maximum values of z_i and Σz_i, respectively (Morton, 1956)] indicates heterogeneity between parents within series, and between the scores in series 1 and series 2 for parents of a given sex, but not between the total score of the mothers versus the total score of the fathers, nor between the total score of series 1 versus that of series

TABLE 5. z SCORES

A. PARENTS SCORED SEPARATELY

("a" totals)

	z at indicated values of θ_1					
	0	.05	.10	.20	.30	.40
Fathers						
Series 1	$-\infty$	−2.8464	−1.7270	−0.7309	−0.2771	−0.0634
Series 2	1.6122	1.4200	1.2140	0.7869	0.3934	0.1071
Total	$-\infty$	−1.4264	−0.5130	0.0560	0.1163	0.0437
Mothers						
Series 1	2.5173	2.2076	1.8849	1.2273	0.6195	0.1697
Series 2	$-\infty$	−1.6943	−1.1136	−0.4957	−0.1892	−0.0431
Total	$-\infty$	0.5133	0.7713	0.7316	0.4303	0.1266
Mothers and Fathers						
Series 1	$-\infty$	−0.6388	0.1579	0.4964	0.3424	0.1063
Series 2	$-\infty$	−0.2743	0.1004	0.2912	0.2042	0.0640
Grand Total	$-\infty$	−0.9131	0.2583	0.7876	0.5466	0.1703

B. FAMILY SCORES ("b" totals)

							$\hat{z}$
Series 1	$-\infty$	−0.5796	0.3709	0.6935	0.4432	0.1349	0.70
Series 2	$-\infty$	−2.0510	−0.6450	0.0227	0.0847	0.0401	0.11
Total	$-\infty$	−2.6306	−0.2741	0.7162	0.5279	0.1750	0.75

TABLE 6. $\hat{z}$ SCORES. GRAPHICAL SOLUTION USING "A" TOTALS

Item	Series 1	Series 2	Series 1 plus 2
Fathers	0	1.90	0.10
Mothers	2.52	0	0.68
Mothers plus fathers	0.50	0.16	0.63

TABLE 7. TESTS FOR HETEROGENEITY

A. Series 1 vs. series 2

Fathers	$X^2_{(1)} = 4.605(0 + 1.90 - 0.10) = 8.29$
Mothers	$X^2_{(1)} = 4.605(2.52 + 0 - 0.68) = 8.47$
Mothers plus fathers	$X^2_{(1)} = 4.605(0.50 + 0.16 - 0.63) = 0.14$

B. Mothers vs. fathers

Series 1	$X^2_{(1)} = 4.605(0 + 2.52 - 0.50) = 9.30$
Series 2	$X^2_{(1)} = 4.605(1.90 + 0 - 0.16) = 8.01$
Series 1 plus 2	$X^2_{(1)} = 4.605(0.10 + 0.68 - 0.63) = 0.69$

C. Family scores

Series 1 vs. series 2

$$X^2_{(1)} = 4.605(.70 + .11 - .75) = 0.28$$

D. Linkage

$$X^2_{(1)} = 4.605(.75 - 0) = 3.45$$

2. Linkage is not significant by the likelihood ratio test ($\chi^2_1 = 3.45$, P = 0.06). The data are presented in tables 7A and B.

In the absence of adequate evidence for linkage, or for heterogeneity between the sexes, or between the series in the pooled data, the heterogenity within series is probably no more than a nonsignificant genetic curiosity. There is no apparent biological reason to lead one to expect or to accept such reciprocal heterogeneity between the parental scores in these two successive series (Steinberg and colleagues, 1956). The absence of a biologically rational alternative tends to support the conclusion that in this case the χ^2 evidence may be ignored (Berkson, 1938, see especially footnote 4, page 531).

Similar reasoning leads us to conclude that the heterogeneity between the scores in series 1 and series 2 for a parent of a given sex is not biologically significant.

The z scores for families are presented in table 5B. There is no evidence suggesting heterogeneity between the two series (Table 7C); hence the scores may be combined. Here again, only recombination as low as or lower than five per cent is excluded. The scores for other values of θ_1 are inconclusive.

The failure of this relatively large body of data to provide decisive scores concerning recombination in excess of five per cent emphasizes the point that linkage studies with recessive genes require much larger samples than most investigators have at their disposal. Indeed, it seems probable that many earlier studies of linkage have had too few data to permit valid conclusions. Therefore it is highly desirable, that all data for linkage studies be published in detail, to make them available for combination with data collected by other investigators.

SUMMARY

The data for linkage studies between the MNS locus and cystic fibrosis of the pancreas published by Steinberg, Shwachman, Allen and Dooley (1956) have been reanalysed using a sequential test for the detection of linkage (Morton, 1955 and 1956).

The method is illustrated in detail and two additional z scores (z_6 and z_7) for matings of types Gg $T_1t \times$ Gg T_1T_2 and Gg $T_1T_2 \times$ Gg T_3T_4 are derived.

Recombination as low as, or lower than, five per cent is excluded with a high probability, but the data are insufficient to reach a conclusion about recombination in excess of five per cent.

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BOOK REVIEWS

A Clinical, Pathological and Genetic Study of Multiple Neurofibromatosis

By F. W. Crowe, W. J. Schull, and J. V. Neel. Springfield, Ill.: Charles C Thomas, 1956. 181 pp. $5.00.

A volume of the American Lecture Series in Dermatology, this work will have great interest not only for dermatologists, but also for geneticists and for physicians in other fields, such as neurology, internal medicine, and pediatrics. It covers 203 cases of neurofibromatosis in 107 families, which include in addition 353 normal relatives; 20 additional cases seen in an institution were added to make 223 in all. The volume of the material, and the thoughtful consideration given it, make this a much more authoritative essay on the disease than many of the rather uncritical reports of smaller numbers of cases with which the literature abounds, and should do much to clear up some of the existing confusion about this condition.

The cutaneous manifestations of the disease are described in some detail, and the authors conclude that a reliable clinical diagnosis can be made in the great majority of cases. It is noteworthy that 78 per cent of the patients had at least as many as six café-au-lait spots of 1.5 cm diameter or over, and that while café-au-lait spots are seen in other diseases and in normal individuals, such a number is hardly ever found. Sarcomatous degeneration in the cutaneous neurofibromata occurred in only 2% of the patients. Biopsies were obtained from 107 persons, and the histopathology of the condition is discussed briefly, with eight illustrations. Amplification of this section of the book, with colored photographs, would have been useful but probably not practicable without greatly increasing its price.

The manifestations of neurofibromatosis in the osseous and central nervous systems are also discussed. The prevailing impressions are confirmed that optic and acoustic nerve tumors as well as other types of brain tumor occur in a small number of cases (under 5% in each instance), but one significantly greater than random expectation. The authors state that it was their clinical impression that many or most of the patients were of lower than average mentality, though seldom of idiot or imbecile level. This is in agreement with other published reports, but one is inclined to wish that more details on this point had been given. The incidence of epilepsy is not discussed, but a frequency of 5 to 10 per cent has been stated by other authors.

One seemingly authentic case of neurofibromatosis and tuberous sclerosis coexisting in the same patient is included. The family history in this case was of tuberous sclerosis only, and it is proposed that the neurofibromatosis occurred by mutation. This is probably the only well-authenticated case of this sort in the literature, and the genetic evidence seems clear that the two diseases, while sharing a number of histopathological as well as clinical findings, are determined by separate genes.

The authors estimate the frequency of neurofibromatosis (in Michigan) at 1 in 2500 to 3300 births, making it less uncommon than many have supposed. Of 137 propositi, 39 are classified as familial and 70 as sporadic, but of the latter only 29 had both parents examined. Anyone familiar with the difficulties of carrying out clinical studies such as this, however, will regard this as thoroughness and diligence with no less than the usual difficulty in contacting and examining relatives. Figures are given for the reduced fertility of persons with the disease, and the mutation rate is estimated at roughly 1×10^{-4} per gamete per generation, which is one of the highest reported for a dominant human gene. In familial cases, the evidence is for dominant transmission with a high rate of penetrance, as generally accepted. Transmission and penetrance in children of presumed mutation cases seem to be similar. The possibility of somatic mutation in 4 cases with localized neurofibromatosis is considered.

Detailed case histories are succinctly but adequately presented, in a separate section, where they are available to readers who wish to appraise them critically, but where they do not confuse the rest of the text.

Comparison of this work with that of Borberg (Clinical and Genetic Investigations into Tuberous

Sclerosis and Recklinghausen's Neurofibromatosis, Copenhagen, Ejnar Munksgaard, 1951, 239 pp.) is inevitable. Both studies reach very similar clinical and genetic conclusions, including those as to the relationship of neurofibromatosis with tuberous sclerosis. The latter disease is, of course, more extensively considered in Borberg's monograph. Borberg's work contains a more exhaustive review of the literature, and is especially admirable when one considers that it was written as a thesis for the medical doctorate degree, as required in Continental universities. Crowe and his co-authors have produced a volume that is not only more readily available to American readers, but is also more readable and lucidly organized. Persons especially interested in the field will of course continue to refer to both.

In summary, this is an excellent monograph on both clinical and genetic aspects of neurofibromatosis, and is highly recommended to geneticists and to physicians in both clinical and academic work.

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Genetics Laboratory Exercises

By ELDON J. GARDNER. Minneapolis: Burgess Publishing Co., 1956. pp. viii + 47, 14 figures. $2.50.

THESE 14 exercises are designed to accompany the introductory lecture course in general genetics. They are based on the author's experience in the Department of Zoology at Utah State Agricultural College. The work is prefaced by eight pages of informal definitions of genetic terms, some of which are not found in most texts. The first session is on probability and χ^2, and succeeding exercises cover Mendelism, mitosis and meiosis, biometrical genetics, and the analysis of human pedigrees. Photographs reproduced in the text are intended to substitute for trihybrid barley heads and other material which may be difficult to obtain; several of the figures are unsatisfactory for this purpose, and some, like the large plate labeled "two dice", are of doubtful value. Questions and problems make up a large part of the manual, as in most "laboratory" sessions in elementary genetics, and this material duplicates to a considerable extent the exercises included in standard texts. However, the instructor who prefers a manual will find this one useful.

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Induced Abortion On Psychiatric Grounds: A Follow-Up Study of 479 Women

By MARTIN EKBLAD, Stockholm; transl. by D. Burton. Acta Psychiat. et Neur. Scandin. Suppl. 99, Copenhagen: E. Munksgaard 1955. pp. 238, 42 tables, Dan. kr. 32.–.

THE catamnestic data presented in this Swedish monograph are based on the psychiatric, reproductive and social histories of 479 native women, who had an induced abortion at the Sabbatsberg Hospital (1949–1950) and, after approximately two years, were reexamined psychiatrically at the Karolinska Institute. The abortions were performed on psychiatric grounds as defined by the Abortion Act of June 17, 1938, and in 52 cases were combined with a sterilizing procedure. The subjects were ward patients referred by the City Sex Guidance Center, which means that they came largely from the lower income groups.

Of the 293 married women who had been living with their husbands, 4% admitted adulterous conception, and 65% had previously had 2–3 children. In addition, 58 women were separated, divorced or widowed, and 128 women were unmarried. All the subjects were free of psychotic symptoms and were of either normal or borderline intelligence. Over one-half (63%) had lived with their

parents until the age of 16, while less than one-half (43%) described the home milieu, during childhood, as inadequate.

Apart from 9 women who had a previous history of schizophrenic (4), confusional (1) or depressive (4) episodes although they were regarded as nonpsychotic at the time of the abortion, no subject had been admitted to a mental institution. Over one-half (278) were classified as immature or emotionally unstable, and the remainder (201), as entirely normal in personality. In only one case was physical illness (pulmonary tuberculosis) recognized as a contributory indication for the interruption of the pregnancy.

According to Swedish law, psychiatric indications for legal abortion in nonpsychotic women may include evidence of social distress, but abortion for purely social reasons is not permitted. In general (nonpsychiatric) terms, the following indications are allowed by the Abortion Act: (1) danger to the mother's life or health because of illness or physical defect (medical reasons); (2) "worn-out mothers" with large families, assumed to be close to the breaking point, and "foreseen weakness" of a degree justifying the assumption "that a woman's physical or mental forces would be seriously impaired by the advent of the child and the care of the child" (medical-social reasons); (3) pregnancies resulting from unlawful coercion (humane reasons); and (4) cases where "the woman or the father of the expected child might with reason be presumed to transmit to the child insanity, mental deficiency or a serious physical disease" (eugenic reasons calling for simultaneous sterilization). The number of legal abortions performed under the Act showed a consistent increase (from 4.5 per 1000 infants born alive in 1939 to 57.5 in 1951). The most pronounced relative increase was in the number of abortions based on medical-social indications (from 3.4 to 60.3% of all legal abortions), with abortions on medical, humane and eugenic grounds decreasing correspondingly.

In the sample studied by the author, only cases with psychiatric indications were considered, although in 7% of them there were pertinent eugenic reasons in addition. The main psychiatric indication was based on an actual or foreseen "psychic insufficiency reaction" to an unwelcome pregnancy and its consequences. Despite the vagueness of this formulation, less than one-half of the pregnant women who came to the Guidance Center received permission for legal abortion. Adequate data on the parents and sibs of the subjects were not obtained.

Most of the case histories are sufficiently detailed to repay careful reading. Even in the author's opinion and irrespective of his inability to find "demonstrable psychic sequelae" in more than a few subjects within two years after the termination, many of the performed abortions served no useful purpose, if only because subsequent pregnancies occurred soon after. Of the 427 nonsterilized women, 37% became pregnant within 24 months, frequently by the same mate (66%). Another undesirable feature was an apparent increase in illegal abortions following the activation of the Abortion Act, an observation ascribed by the critics of the law to an "abortion mentality which extends to all women who have become unintentionally pregnant." The author's assumption that 3% of the subjects might have committed suicide while 18% would have had recourse to illegal abortion if their pregnancy had not been legally terminated, is obviously speculative. In any case, 48% of the subjects stated retrospectively that they would have given birth to the child if legal abortion had not been granted.

Substantial reservations are also warranted with respect to the author's conclusion that feelings of guilt, although frequently observed after a legal abortion, especially in "psychically abnormal" women, are rarely so severe as to have an adverse effect on their working capacity. According to his analysis, only one-quarter of the subjects expressed self-reproaches, either of a moderate (14%) or a marked (11%) degree, while another 10% remembered the operation itself as "unpleasant." No evidence of a self-condemnatory trend was found in the remaining subjects after two years.

From a psychiatric standpoint, this study—although it is of unquestionable interest and promise—leaves various basic questions unanswered. Its main shortcomings lie in the selective nature of the sample, the exclusion of psychotic cases, the limited observation period before and after operation, and the conflux of psychiatric and social indications for abortion. Besides, the Swedish and American systems of psychiatric classification are clearly at variance.

The social, forensic and eugenic implications of the Swedish Abortion Act remain outside of the scope of this report. It should be noted, however, that considerable doubt is cast by the author's findings—at least, indirectly—on the efficacy of the criteria used in the current application of the law.

Generally speaking, a critical reader is left with the impression that an educated and fully cooperative society is needed for a constructive approach to the broad problems which a law such as this is expected to solve. The attempt to deal with psychiatrically or eugenically undesirable pregnancies by means of legalized abortion is as unsatisfactory a method as the prospect of bailing out a sinking boat with a teacup. Preventing an undesired pregnancy is safer and more reasonable than permitting its interruption on psychiatric grounds, which means that legal abortion should never be more than a last resort. In a morally responsible society, the main objective should always be a well-organized public public health system, providing adequate facilities for eugenic education, marriage and parenthood counseling, and psychiatric guidance in the management of community problems.

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Letter to the Editor

March 19, 1956

To the Editor
Dear Sir:

Since the original suggestion by Sir Francis Galton, the usefulness of twins in human biological research has been steadily increased by advances in the science of genetics. With rare exceptions, there is now universal recognition of the importance of classifying twins according to their derivation from one or from two fertilized ova. The terms *monozygotic* and *dizygotic*, originated apparently by Arey (1922 Anat. Rec. 23: 245–248) to designate these two types of twins, are cumbersome, and there is a growing tendency throughout the English-speaking scientific world to substitute *monozygous* and *dizygous*. There is something to be said for allowing Nature to take its course, even in the evolution of scientific words, but before this particular trend becomes irreversible, certain considerations should perhaps be weighed by the scientists concerned.

First, the words monozygotic and dizygotic have priority. This is probably the least important argument.

Second, the point of central interest in the distinction between types of multiple birth is the number of distinct genotypes represented, and this corresponds unequivocally to the number of zygotes after fertilization. This is the basis for Arey's terms, which consist of a numerical prefix and the complete stem for *zygote*. The alternate words, monozygous and dizygous, refer to the process of zygosis. Although zygosis is, indeed, essential to the formation of a zygote, the phenomena of twinning can be understood most simply in terms of the number of zygotes and without reference to the complex process of gametic union. In contrast, the shorter stem is quite appropriate in the terms homozygous and heterozygous, which clearly relate to zygosis in that they specify the similarity or dissimilarity of the uniting gametes with respect to given genetic loci.

Third, the major consideration in questions of terminology should be effectiveness in communication. *Monozygous* and *dizygous* have one less syllable and one less letter than the conventional terms, but ease of speaking and writing should not, at least in scientific vocabulary, take precedence over ease with which related terms can be distinguished. The extra effort required to write or to say *monozygotic* and *dizygotic* appears to be less objectionable than the difficulty of avoiding confusion among the four terms ending in *-zygous*. That human geneticists themselves can make this kind of error is illustrated by the following quotation from one of our most respected colleagues:

"The observations were in excellent agreement with expected values calculated on the hypothesis that the monozygous state of a simple recessive gene would condition susceptibility . . .".

Terms that can be confused by specialists are certain to confuse nonspecialists, particularly in a terminology that is already difficult. Indeed, one commonly en-

counters people working in fields related to human genetics who confuse not only the words, *homozygous* and *monozygous*, but also the two quite unrelated concepts. Confusion of the concepts would be avoided by an adequate and consistent terminology.

Whether this matter is to be decided arbitrarily or by usage, it seems to deserve general attention.

Sincerely yours,

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